IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS, CORPORATION,	)	Trial Volume 2
Plaintiff,	)	
	)	C.A. No. 11-1077-RGA
v.	)	
PAR PHARMACEUTICAL, INC.,	)	
Defendants.	)	

Friday, May 2, 2014
8:10 a.m.

844 King Street
Wilmington, Delaware

BEFORE: THE HONORABLE RICHARD G. ANDREWS
United States District Court Judge

APPEARANCES:

McCARTER & ENGLISH, LLP
BY: DANIEL M. SILVER, ESQ.

-and-

FITZPATRICK CELLA HARPER & SCINTO
BY: NICHOLAS N. KALLAS, ESQ.
BY: CHARLOTTE JACOBSEN, ESQ.
BY: DOMINICK A. CONDE, ESQ.
BY: DANIEL MINION, ESQ.
BY: CHRISTOPHER LOH, ESQ.

Counsel for the Plaintiff

APPEARANCES CONTINUED:

RICHARDS LAYTON & FINGER, P.A.
BY: STEVEN J. FINEMAN, ESQ.

-and-

LATHAM & WATKINS, LLP
BY: DANIEL G. BROWN, ESQ.
BY: JENNIFER KOH, ESQ.
BY: ROGER CHIN, ESQ.

Counsel for the Defendant

THE COURT: Good morning. Are we ready to proceed?

MR. KALLAS: Yes, Your Honor.

THE COURT: Before we proceed, Mr. Chin, is there somebody on the Par side, the three depositions that were played at the end of yesterday, what was their relevance?

MR. CHIN: So the three depositions are being offered for the invalidity part of the case.

THE COURT: All right. And they are relevant how? I understand the invalidity, I understand what part of the case. What do they have to do with invalidity?

MR. CHIN: They demonstrate that with respect to the full scope of the claims that the inventors themselves were unable to get one of the identifying products to work and did not know about the others.

THE COURT: All right. Okay. Let's go.

MR. CHIN: We have one issue with an exhibit that we need to correct.

MR. FINEMAN: No dispute, Your

Honor, just to correct something. Page 205 of the transcript there was a discussion of the JTX 187. JTX 187 was not admitted. Par moves JTX 187. I understand there is no objection.

MR. KALLAS: No objection, Your Honor.

THE COURT: JTX 187 is admitted without objection.

MR. FINEMAN: And two other clarifications, Your Honor. I'm speaking on behalf of both sides. I believe that in the record, JTX 078 appears as JTX 68, so it should be 78. And PTX 343 appears as 363.

THE COURT: Well, both parties agree, that's a good thing to talk to the court reporter about and they can make those changes, but it's now on the record.

All right. Are we ready to proceed?

MR. CHIN: I believe we are. Par calls Dr. Michniak-Kohn.

THE COURT: I did look at her resume.

MR. CHIN: May I approach to hand up a couple of binders?

THE COURT: Sure.

THE CLERK: Please state and spell your full name for the record.

THE WITNESS: My name is Bozena, that's B-O-Z-E-N-A, Michniak-Kohn, and that's M-I-C-H-N-I-A-K - K-O-H-N.

BOZENA MICHNIAK-KOHN, PH.D.,
the deponent herein, having first
been duly sworn on oath, was
examined and testified as follows:

MR. CHIN: I just need to get copies for everybody.

THE COURT: That's all right.

DIRECT EXAMINATION

BY MR. CHIN:

Q. Good morning, Dr. Michniak-Kohn. Could you please introduce yourself to the Court?

A. Yes. I'm Dr. Bozena Michniak-Kohn. I'm a professor of pharmaceutics at the Ernest Mario School of Pharmacy at Rutgers University in Piscataway, New Jersey. And I'm also the director for the Center for Dermal Research as well as the director for the lab for drug

delivery of the New Jersey Center for Biomaterials, that's also Rutgers University.

Q. What is your area of expertise?

A. So my area of expertise is transdermal and topical pharmaceutical dosage forms and dosage forms in general, and in particular formulations such as transdermal patches, lotions, ointments, nano carriers and topical formulations. And in addition I'm familiar with the standard testing methodologies that are used in the pharmaceutical industry.

Q. Could you turn to DTX 534 in your binder.

A. Yes, I can.

Q. What is this document?

A. This is my CV.

Q. Does DTX 534 provide an accurate summary of your professional credentials?

A. Yes, it does.

MR. CHIN: Par moves the admission of DTX 534 into evidence.

MR. CONDE: No objection.

THE COURT: Admitted without objection.

MR. CHIN: And Par also offers Dr.

Michniak-Kohn as an expert in transdermal drug forms and pharmaceutical standards for evaluating drug products.

MR. CONDE: No objection with a qualification that that doesn't include statistic as her expertise.

THE COURT: All right. Mr. Chin.

MR. CHIN: Perhaps we need to cover that area.

THE COURT: I think so, the rest of it is fine.

THE COURT: I mean, the rest of it is fine, but if she is going to testify about statistics, I think you better lay a little more foundation.

BY MR. CHIN:

Q. Dr. Michniak-Kohn, do you use statistics in your work in testing pharmaceutical products?

A. Yes. In fact, for all of my publications, et cetera, we constantly, in every day, use statistics for all of the evaluations of any data.

Q. What is your role in setting up statistical plans for pharmaceutical studies that

you conduct and supervise?

A. Well, I basically work with statisticians or work by myself to evaluate what the design of experiments will be for any particular study. Depends how big it is and what kind of study it is, but I use that constantly.

And I've, obviously, been educated in statistical analyses because that's part of any basic scientist's work.

Q. Do you use statistical reference books in your own work?

A. Of course. I've got several at my shop?

MR. CHIN: Your Honor, we would offer Dr. Michniak-Kohn, also, as an expert in pharmaceutical testing, to the extent that that encompasses statistics. We're not offering her as statistics expert, per se.

THE COURT: All right. I understand that.

Is there any objection?

MR. CONDE: No objection with that qualification, Your Honor.

THE COURT: Okay. Thank you, Mr. Chin.

And, again, I'm sorry the gentleman for Novartis, who are you?

MR. CONDE: Dominick Conde.

THE COURT: Conde?

MR. CONDE: Conde, yes, sir.

THE COURT: Okay. Go ahead, Mr. Chin.

BY MR. BROWN:

Q. Dr. Michniak, what were you asked to do in this case?

A. I was asked to look at some reports that Dr. Davies had submitted and see if there was any evidence for the oxidative degradation -- acetaldehyde to perform any oxidative degradation.

Q. And what did you conclude?

A. If I could have my first slide, please.

So, first of all, Dr. Davies' experiments were flawed and really didn't show that acetaldehyde reduces oxidative degradation. There are three main points that we need to consider and that is: First of all, that the Dr. Davies' experiment did not model conditions of a transdermal patch.

Number two, inappropriately added

peroxide, even though Par's ANDA products are substantially free of peroxide.

And, finally, fails to show any statistically significant results.

Q. I understand you were not available to attend trial yesterday due to your professional obligations, but did you have an opportunity to at least review the -- briefly review the transcript of Dr. Davies' testimony from yesterday about his experiments?

A. Yes, I did.

Q. And did you also have an opportunity to study the data and reports that Dr. Davies generated in connection with his experiments?

A. Yes, I did.

Q. I'd like to focus on the first bullet point, and if we could have that highlighted. It states that the Davies' experiment does not model the conditions of a transdermal patch.

What type of dosage form is Par's product?

A. The Par product is a transdermal drug delivery system. In other words, a patch.

Q. Can you turn to JTX 068 in your binder?

Do you recognize this document?

A. Yes, I do.

Q. What is this document?

A. This is the proposed draft package insert for the Par ANDA product, the Rivastigmine transdermal drug system.

MR. CHIN: Your Honor, Par moves for the admission of Exhibit 068.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MR. CHIN:

Q. I'd like to turn to Page 221. And, in particular, the diagram near the bottom.

Layer two is labeled drug-in-adhesive (acrylic) matrix. What is the drug-in-adhesive matrix in Par's product?

A. So layer two or the drug-in-adhesive (acrylic) matrix is basically a mixture of long polymer chains in which the active agent, the Rivastigmine, is uniformly distributed. And it has another action as well, because it's obviously a drug-in-adhesive.

So that portion of the patch sticks the patch onto the skin of the patient when it's put on.

Q. What happens when the patient removes the backing and applies the patch to their skin?

A. So when they remove the backing, obviously the first thing is it sticks to the skin. And then the second thing is that the Rivastigmine now has a chance to exit the patch.

And we basically create what is known as a concentration gradient because it's a high level of Rivastigmine in the patch. Nothing on the skin at the beginning.

So there's a big driving force to drive the Rivastigmine out of the patch into the -- into the skin. And, obviously, into the systemic circulation of the patient.

Q. What did Dr. Davies' test in his experiment?

A. Dr. Davies tested a solution of Rivastigmine.

Q. Does it matter that Dr. Davies tested a solution instead of a transdermal patch?

A. Absolutely. Because, as we see, the

transdermal patch is more of a solid system with this network of polymers. And Dr. Davies tested a solution and those two environments are different from each other.

So there are no -- there was no relevance. And, in fact, in each of those environments, the chemical kinetics are going to be very, very different.

Q. Now, what do you mean by kinetics?

A. If I can have the next slide, please.

So reaction kinetics concerns two things. They concern the rate of a reaction and the properties of that, and also the activation energy of chemical reactions.

Now, what I mean by that, just to explain it, it really means whether a reaction would proceed at all and whether it would happen in either environment.

And there are three factors that affect reaction kinetics.

Number one, it's the degree of contact between molecules, the physical state of the medium. And I know I'm using a lot of words here.

So to put it in more simple terms, the physical state of the medium would be whether it's a solid, a liquid or a gas. We won't be considering gases.

Secondly, the temperature.

And, thirdly, the concentration of the substances in the medium.

Q. How does Par's product compare with the Davies' experiment with respect to these reaction kinetics?

A. If I can have the next slide, please.

So, in this slide, what I did is I took those three kinetic factors. So we see on the left-hand side that we've got physical state contact listed, temperature and concentration. And then the green refers to the transdermal patch or Par's ANDA product. And the orangey pink refers to the conditions in Davies' experiment.

Q. Let's focus on the first kinetic factor, physical state and contact. How does the first factor affect reaction kinetics?

A. So we notice that in these two situations, we're actually talking about a particular

physical state. So we're talking about a solid or a liquid.

So, in a liquid, molecules are able, in fact, to move around much faster and they're freer to move around, whereas in a solid, they have more restrictive movement. So it's more difficult for them to move.

So it's more difficult for them to move. So by looking at liquids, acetaldehyde, for example, probably could react more likely in a liquid solution than it would be when it's immobilized in a patch.

Q. And with respect to the first kinetic factor, how does Dr. Davies' experiment compare with the transdermal patch?

A. As I just mentioned, Dr. Davies used a liquid solution and definitely in that state with those acetaldehyde molecules it would be more likely that you could -- you would see a chemical reaction than you would ever see in a solid structured polymatrix that's present in the Par ANDA product.

Q. And taking your second kinetic factor can you explain how temperature affects the reaction

of kinetics?

A. It's generally known in science that the higher the temperature the faster the chemical reaction rates proceed and there is a general rule that for every increase in ten degrees centigrade, you can double reaction rates.

And again, just to illustrate it with a simple example, if we take cookie dough and we just leave it out at room temperature, nothing much happens, but if you increase the temperature, you put it in an oven, you can even have a short period of time and hopefully you get cookies at the end. What that is trying to illustrate basically is that conditions are very important and high temperatures can encourage reactions to happen. Whereas in a solid situation, in a low room temperatures that may not happen at all.

Q. Can you turn to JTX 68 in your binder. This is the label that we just looked at a bit earlier and I would like to turn to page 233 this time. Does this provide information about the temperature under which the Par product is to be stored?

A. Yes. If we look halfway down that slide, it says how should I store rivastigmine transdermal system. And we're told that we have to store rivastigmine transdermal system at 59 degrees Farenheit to 86 degrees Farenheit, 15 degrees centigrade to 30 degrees centigrade, essentially what that means is at room temperature.

Q. And can we turn back to slide number five. With respect to the second kinetic factor, how does Dr. Davies's experiment compare with the Par transdermal patch?

A. So again, comparing Dr. Davies's experiment, Dr. Davies used a rather high temperature of 140 degrees Farenheit, 60 degrees centigrade, whereas Par's ANDA products are stored at room temperature so it was more likely in the Davies experiment that any molecules would have a chance to react.

Q. And taking your third kinetic factor, can you explain how concentration affects reaction kinetics?

A. So again a general rule in science is that the higher the concentration the more likely you

have a chance of a chemical reaction, in other words, you have more molecules so if you have more molecules are they're more likely to react.

So again, in conclusion, if you have high concentrations and I can probably give you an illustration, nitroglycerin, if we have a high concentration of nitroglycerin then we have an explosive situation, it's an explosive mixture, but nitroglycerin at very high dilute concentrations or low concentrations is used for patients to treat angina and we don't have bombs going off.

So in conclusion, the concentration makes a big effect. It's in every equation in science. The more you have of a certain molecule, the more likely it is to be able to react.

Q. And can you briefly describe the concentration of the Par components of the Par products?

A. Yes, I can. If I can have the next slide, please. So what I've listed here on the left we have the components, and then on the right we have the amounts, and we have rivastigmine listed,

which is obviously the reactive agent.

The acetate copolymer adhesive and the isopropyl myristate, if you take them from the slide, acetate copolymer adhesive is the highest concentration, 74 percent.

Q. Can we turn back to slide number five. With respect to the third factor, how does Dr. Davies' experiment compare with the Par product with respect to the excipients?

A. So we just saw from a previous slide that the Par's transdermal patch contains adhesive in the fact that the adhesive is in high concentration. Dr. Davies' experiment on the other hand omitted both of those components totally, and none was present, and the conclusion from that is that by missing those components of course, those molecules didn't have the adhesive and the tackifier to work into, so again the likelihood of anything happening with molecular reaction rates in the Davies experiment was much higher.

Q. And how does Dr. Davies' experiment compare with the Par product with respect to peroxides?

A. Well, first of all, the Par's transdermal patch is substantially free of peroxides, whereas in the Dr. Davies experiments he added a large amount of peroxide, in fact he added TBHP which is not even present in the Par ANDA products. So again we have two radically different environments here comparing Dr. Davies' experiment and what actually happens in the transdermal patch.

Q. And can you turn to JTX 53 in your binder?

THE COURT: Actually, Mr. Chin, on the third point there, you said the greater the concentration the more the reaction, general rule of science; right?

THE WITNESS: Correct.

THE COURT: And so what is there a greater amount of concentration in Dr. Davies' experiment than in the transdermal patch, there was a greater concentration of what?

THE WITNESS: No. On that point I was discussing the concentration of the excipients and the fact that there were excipients in the transdermal patch but none in the Davies' experiment. But in general if you

have more of -- in theory, we're covering both of these points, sorry, Your Honor, both the excipients and the peroxide because if you have a large amount of peroxide and that was my next point, you have a high concentration of the peroxide, lots of molecules so you would get a high reaction.

THE COURT: So it's not the absence really of the adhesive and the tackifier, and other than the fact that we talk about the peroxide, that means the concentration of the peroxide is greater?

THE WITNESS: I was trying to give you the theory first on what the effect of greater concentration is, so the more molecule you have, the more likely it is to react. However, I broke these down to excipients and peroxide, and looking at the adhesive which is in high concentration, it's not there in the Davies experimental all.

THE COURT: Okay. I got your point. Thank you.

BY MR. CHIN:

Q. And Dr. Michniak, does the presence of a

large amount of adhesive in the transdermal patch have any affect on any reaction between acetaldehyde and other components?

A. Of course because the facts and we covered that the adhesive is actually high concentration and that is that polymer network making it more of a solid component, so of course in that environment those molecules are far less likely to meet each other and reacted than they would be in a solution that's lacking all of these solid like polymer network.

Q. Turning to the issue of peroxides, could you turn to JTX 53 in your binder. Do you recognize this document?

A. Yes, I do.

Q. And what is it?

A. This is Dr. Davies' experiment on looking at the peroxide content in Par's adhesives and excipients.

Q. And what does Dr. Davies' data show?

A. Well, if we take that document and look at the very last page, there is a table there on the section B, and what we see there is on the left-hand side there are listed raw ingredients.

Basically what Dr. Davies did is he took the raw ingredients that are included in Par's transdermal patch and the acetate copolymer adhesive and the isopropyl myristate and the peroxide values are listed we see that the acetate copolymer adhesive we have 1.12 and 1.16 and for the isopropyl myristate we have 0.9 and 1.12.

Q. What does these ranges mean?

A. Actually those values are extremely low. In fact, we can say that these raw materials are substantially free of any peroxide at all.

Q. Can you turn to JTX 74 in your binder. And this patent has been

BY MR. CHIN:

Q. And this patent has been previously admitted into evidence. Do you recognize this document?

A. Yes. It's the US patent '498, the LTS Lohman patent that discusses peroxide numbers.

Q. Can you turn to Column 6, Lines 8 through 20? What does this passage describe?

A. So what we see in this passage is that it's talking about a transdermal therapeutic

system. And then if we look at line, I think it will be, 13 in the middle there, it talks about substantially free of hydroperoxides.

And hydroperoxides are a type of peroxide. So we see the statement that I actually just used.

If we look towards the end of that, the bottom of that slide, we see a reference to peroxide numbers, PON, of not more than 20, preferably not more than ten with particular preference, not more than five.

So what we're learning here that in this patent, there is an explanation of what substantially free of hydroperoxide means. And those high values means that or it gives an explanation of how peroxide values and substantially free of hydroperoxides are related.

Q. And what does this passage tell you about peroxide numbers of the range 0.9 from 1.16 that we were discussing previously?

A. So those values in the raw ingredients that are use for the Par ANDA product were extremely low. And, in fact, I correctly used that term, substantially free of peroxides.

Q. Can we turn back to Slide 5?

How does the amount of peroxide that Dr. Davies measured in the raw materials used in the Par product compare to the amount of peroxide that's used in his experiment?

A. So, as I mentioned previously, a large amount of peroxide was used in the Davies' experiment, the TBHP. It was about 10,000 times what would ever be present in the Par transdermal patch, which we decided is substantially free of peroxides.

Q. And how does that affect the possibility of any reaction with peroxide in acetaldehyde?

A. Well, we see that the environment, as far as peroxide is concerned, is drastically different. If you have 10,000 times of something in one environment and hardly anything in the other, then that's a big difference. So we cannot extrapolate from one model to or from the Davies' model to the transdermal patch.

Q. Can we turn back to your summary slide, Slide 303?

We've covered the first two bullet points, I believe. And I'd like to focus on your

third bullet point, fails to show any statistically significant results.

At the time that Dr. Davies conducted his study, how did he analyze whether or not his data showed any statistical significance?

A. He used the one-sided T test.

Q. What is a T test?

A. A T test basically is a statistical method that you use to determine whether there is a difference between two sets of data. Usually a control set and the test set.

And basically it's dangerous to look at data like that. And, for example, I saw some bar charts and some slides from yesterday where, you know, scientists can, of course, draw bar charts. But you cannot look at bar chart and then see a difference and then say, There will be a difference because that's deceiving.

So, in fact, what should be done is a proper statistical analysis of the data before you make any conclusions.

Q. In your opinion, did Dr. Davies' experiment show any statistically significant

antioxidant effect of acetaldehyde?

A. In my opinion, no, it didn't because it wasn't statistically significant.

Q. And how did you reach that conclusion?

A. Well, he used a one-sided T test where he should have probably properly used a two-sided T test.

Q. Can you turn to DTX 540 in your binder?

Do you recognize this document?

A. 540. Yes, I do.

Q. What is this document?

A. This is a book by Altman called Practical Statistics for Medical Research.

Q. Do you presently use this book in your own work on statistical analysis in pharmaceutical testing?

A. Yes. Among the very many books on statistics that I have on my shelf, I have this book.

Q. Is this textbook considered a reliable authority in the research community?

A. Absolutely.

MR. CHIN: Par moves for the admission of DTX 540 into evidence.

MR. CONDE: No objection.

THE COURT: Just as a matter of curiosity, is this the entire book or --

MR. CHIN: No, it's an excerpt.

THE COURT: Okay.

MR. CHIN: We can save some space on your shelf.

THE COURT: I'm sorry. Admitted without objection.

BY MR. CHIN:

Q. Can you turn to Page 171?

I'd like to focus on the top half of the page. What does this passage in the statistics textbook describe?

A. So if we look towards the second paragraph in the middle of the page, we see a reference to what we just talked about, the one-sided tests and it says that one-sided tests are rarely appropriate.

And, in fact, if we read on after this, it says that even when we have strong prior expectations of an outcome from comparing those two sets of data, we cannot be sure that we're right. So, even if you do have that, you really

scientifically should not make assumptions and prejudge yourself.

And what this passage also tells us, that if we look at the top of this slide, it refers to a two-sided T test. And the sentence after that tells us that, in the vast majority of cases, this is the correct procedure to use.

Q. How do these principles apply to Dr. Davies' statistical analysis?

A. Well, first of all, Dr. Davies' used a one-sided T test, which we see from here that it's probably not the best choice. There are very rare circumstances where you might have a strong prior expectation.

But we know about acetaldehyde. We have a dispute right now.

So we don't know and we shouldn't make that prejudgment. So the correct approach would have been for Dr. Davies to say, I can't prejudge. I shouldn't be doing it and I should have done a two-sided T test.

Q. Did you analyze Dr. Davies' data using a two-sided T test?

A. I did. And if I can have the next slide.

So what I did in this slide is I've listed the time, the 6 hours, 15 hours, 21 hours and the Impurity 4, EVAC and the Rivastigmine. This is straight out of Dr. Davies' report.

And I recalculated the P-values according to a two-sided T test.

Q. What is a P-value?

A. So, a P-value is a way, again, of telling the difference between those two sets of data that -- the control and the test. And a P-value of P equals 0.05 or less is considered by the entire scientific community as being statistically significant.

So the idea is you don't draw those bar graphs and look at differences visually, even though you might see a difference. You really have to apply a test.

You calculate your P-value and then say, Is it equal or below .05?

So that's standard across the board. So what I did when I received Dr. Davies' report is I basically saw the one-sided T test and realized that that's absolutely not the way to go.

And I recalculated things with those -- these P-values. And as we see, looking at those nine numbers, that the lowest number is .051 and the highest is .130. That's the range.

And, in fact, all of those nine points basically, according to any scientist, are not statistically significant.

Q. In your opinion, could you draw a scientifically reliable conclusion from data that is above 0.05?

A. Absolutely not. In fact, the scientific community has decided that that is the bar that every peer-reviewed paper looks at, every study looks at and most all scientists consider that to be the right approach.

Q. And although you were not able to attend trial yesterday, did you have an opportunity to review Dr. Davies' slides?

A. Yes, I did.

Q. And can we take a look at PDX 144, which is Dr. Davies' summary of his statistical analysis.

Does Dr. Davies' statistical analysis demonstrate that he obtained

statistically significant results?

A. No, it doesn't illustrate at all that he got statistical significance because, obviously, he used a one-sided T test analyzing his data.

And, of course, the problem with that is that you really have to do one test when you design your experiments at the beginning. What he did is go back and do all of these other tests and basically massage the data.

Because you're really not allowed to do statistics after you've got the data because it introduces bias, because you can look at the data and then say, Well, I'm going to try, you know, four tests and see which one might give me statistical significance.

That's an absolute no-no. The way you design an experiment, you start at the beginning.

You say, This is my hypothesis. This is the appropriate statistical analysis that I should be doing and then I run the experiment.

I shouldn't be running the experiment and then saying, You know, it didn't quite work the first time, so I'm going to go

back and find a test that I can match and get statistical significance.

That's absolutely not the way to go.

Q. And is this rule about changing the statistical analysis something that's recognized in the industry?

A. Absolutely. In fact, you know, pharmaceutical people working in the pharmaceutical industry are scientists. So it's a basic scientific principle.

And, in addition, of course, if we look at clinical trials, I mean, that's a good example probably. You know, the FDA even mandates before you do a clinical trial that you make the hypothesis in what you're planning to do. Obviously, design the experiment correctly, but also to plan your statistics before you run the clinical trial.

We'd be in a lot of trouble if people did the clinical trial and then said, You know, on this drug, then they went back and did a statistical test and said, Oh, my drug works. And, in fact, really it did not work. We would really be in trouble.

Q. I'd like to recap some of the issues that you raised in your testimony today about Dr. Davies' experiment. If we could turn back to Slide 5.

Here you pointed out a few differences you identified between the transdermal patch and the Davies' experiment. Starting with the first variability, physical state and contact, how did that approach taken by Dr. Davies affect the results?

A. So Dr. Davies' approach basically was bias in favor of finding an antioxidant action because he chose to use a liquid solution rather than using the actual product, the transdermal patch or even a version of that, he went straight to a liquid, so again we can't extrapolate from the Davies experiment to what's happening or may be happening in the transdermal patch.

Q. And next is temperature, how did the approach taken by Dr. Davies affect the results?

A. Again, Dr. Davies' approach was bias in finding an antioxidant action because he conducted his experiment at a much higher temperature and we decided that higher

temperatures speed up chemical reactions. So again, we can not extrapolate what happens in the Davies experiment versus what may or may not happen in Par's ANDA product.

Q. And next is the concentration of excipient. How did the approach taken by Dr. Davies affect results?

A. So, again, to recap that Dr. Davies' approach was again bias because in favor of finding an antioxidant action because he totally omitted one of the major components of the transdermal patch, he had no adhesive, no tackifier in his experiment so we can't extrapolate and compare those two situations. We have got two totally different environments.

Q. Next is peroxide, how did the approach taken by Dr. Davies affect the results?

A. Again, Dr. Davies' approach was bias in favor of finding an antioxidant action because he added a large amount of peroxide when we know that the Par ANDA product is substantially free of peroxide. So, again, those two situations cannot be compared.

Q. And finally we discussed statistical

tests. How did the one-sided T-test taken by Dr. Davies affect results?

A. So Dr. Davies' approach was bias in favor of finding an antioxidant action because by using a one-sided T-test not only was he incorrect, but a one-sided T-test allowed him to find statistical differences and that's generally true if you do a one-sided T-test, it allows you to sometimes to find statistical differences that aren't real at all. So again, we can't extrapolate.

Q. And in your opinion, does Dr. Davies provide evidence that acetaldehyde reduces oxidative degradation?

A. Sorry. Could you repeat.

Q. In your opinion, does Dr. Davies provide evidence that acetaldehyde reduces oxidative degradation?

A. Absolutely not, because first of all, the Davies experiment was a totally wrong model for the transdermal patch. Those two situations are very, very different as we learned today.

And number two, his statistics was totally wrong so he found statistical difference

where there wasn't or used the wrong test, in other words. And finally, he had a totally systemic bias in all the design of experiments he did in favor of finding an antioxidant action.

MR. CHIN: Thank you. I have no further questions.

THE COURT: Thank you Mr. Chin.

Mr. Conde.

MR. CONDE: May I approach, Your Honor?

THE COURT: Yes.

CROSS-EXAMINATION

BY MR. CONDE:

Q. Good morning, Doctor.

A. Good morning.

Q. Chemistry is not something you're comfortable opining on; correct, Doctor?

A. Depends on how you define chemistry. My degree is not in chemistry, but my degree is in pharmaceutical sciences that includes a large -- a lot of chemistry.

Q. You don't recall saying at your deposition that chemistry is not something you're comfortable in opining on, Doctor?

A. Again, depends on what you're talking about chemistry. I am not a synthetic chemist and I don't do synthetic chemistry, definitely.

Q. And the chemistry aspects of this case is not something you researched in forming your opinions; correct?

A. Again, depends on how you define chemistry.

Q. The organic chemistry aspects of this case; correct?

A. Organic synthetic aspects.

Q. And as to Par's products, you do not know how the adhesive used in Par's product is prepared; right?

A. I do know because I have seen a lot of materials and reviewed a lot of supplemental materials on how these types of polymers are prepared.

Q. And you don't talk about how these polymers are prepared in your expert report; right?

A. As far as I can recall, no, but I did look at materials about this.

Q. Now, at the end of your direct testimony,

you identified five things that you criticized Dr. Davies' testing on. Do you recall that?

A. Yes, I do.

Q. You have not done any testing to confirm that your criticisms are correct; right?

A. I was not asked to perform any testing. I mean, if I was, I may have accepted the offer.

Q. So you didn't volunteer to do any testing to confirm that any of those criticisms that you gave at the end of your direct testimony were accurate; right?

A. Well, I was asked to opine on materials on a study of Dr. Davies' work, but I'm a busy person as well, so I didn't volunteer.

Q. And you have not done any analytical testing on Par's ANDA product; right?

A. No, I did not do any analytical testing, but again, I reviewed a lot of materials that concerned the Par's ANDA product and the testing that was done.

Q. But you did not yourself do any analytical testing on Par's product; correct?

A. Did I go to the lab and do any testing? No, I did not.

Q. And I think you testified at your deposition that you could have repeated Dr. Davies' testing; right?

A. Well, I could have put rivastigmine and made the solution, of course.

Q. And you could have repeated his testing; right?

A. If I had every single detail and information, one assumes that an experiment can be repeated.

Q. And you did not make any attempt to repeat Dr. Davies' test; right?

A. No, I was not asked to repeat any tests.

Q. And you didn't volunteer to repeat his test, did you?

A. Again, I'm rather busy, so if I'm not asked, I probably wouldn't have volunteered.

Q. We will stipulate that everyone is busy. You didn't volunteer to repeat Dr. Davies' test; right?

A. I wasn't asked to, so I didn't volunteer.

Q. Now, much of your testimony went to the issue of whether Par -- whether acetaldehyde functioned as an antioxidant in Par's patch;

right?

A. Correct.

Q. And you know that Claim 7 isn't directed to the function of acetaldehyde in Par's patch; right?

A. I don't -- you would have to point me to what Claim 7 exactly is.

MR. CONDE: Can you put Claim 1. Could you please put up the demonstrative with the definition of antioxidant.

BY MR. CONDE:

Q. So are you familiar with the Court's claim construction as to the term antioxidant?

A. Yes, I recall seeing the claim construction.

Q. And you know that that construction does not include a function element to it; right?

A. I don't recall exactly what the exact wording was.

Q. Let's see if we can put the exact wording up on the screen. Bear with us for a moment, please. So if we look up on PDX 105, it says antioxidant requires the presence of an agent that reduces oxidative degradation. Are you

familiar with that definition, Doctor?

A. Yes, I am.

Q. And it does not require a function element, does it?

A. Could you define function?

Q. It doesn't use the word function, does it?

A. No, it doesn't use the word function.

Q. And also you discussed a lot about peroxides on your direct; correct?

A. Yes, I did.

Q. And Claim 7 doesn't require plaintiffs to prove that there are any peroxides in Par's product; right?

A. Again, I am not familiar with exact wording on Claim 7.

Q. We can put the whole claim back up. Would you please do that, Mr. Hoy. And we're on PDX 103. There is Claim 7.

Claim 7 doesn't recite the need to prove that there is a peroxide in Par's product; right, Doctor?

A. No, I don't see the word peroxide there.

Q. Mr. Hoy, could you please go to JTX 74 which is the '498 patent. And I believe this is

also in your exhibit book, but it probably would be easiest just to follow it up on the screen.

Could you first start at the place that Dr. Michniak-Kohn started in her direct. Let me get the right cite which as at column five line -- I'm sorry. My apologies.

A. It was actually column six.

Q. Thank you. Column six, lines eight to about 20. And you cited to this, this column and these lines in support of your opinions; right, Doctor?

A. Yes, I did.

Q. So now let's leave this and go to column seven, line eight in the same patent. And at column seven, line eight in the '498 patent says, "Following this treatment, the materials are virtually free from peroxides and may be used without concern even if loaded considerably beforehand."

Do you see that?

A. Yes, I do.

Q. And it goes on to say, "An additional improvement in stability may be achieved by the addition of antioxidants which retard or suppress

the formation of new peroxides during the storage of the systems."

Do you see that?

A. Yes, I do.

Q. So the '498 patent acknowledges that even after you do the treatment, one could still add antioxidants; right?

A. Yes, it does.

Q. Now, in your direct, you talked about Dr. Davies' testing and the fact that he used a peroxide to do the testing, the stress test; right?

A. Correct.

Q. And you agree that peroxides can cause the oxidative degradation of rivastigmine; right?

A. In general or in a certain situation?

Q. Let's start in general.

A. Yes, in general, in chemistry, yes.

Q. And one of the techniques used by pharmaceutical companies to assess oxidative stability by stress testing is to use peroxides; right?

A. Correct.

A. Correct.

Q. And a lot of articles mention the use of peroxides to conduct oxidative degradation stress testing; right?

A. There are all articles, indeed.

Q. Right. And the specific peroxide that Dr. Davies used was T-butyl hydroperoxide; right?

A. Correct, was the TBHP.

Q. And TBHP was actually mentioned in the '498 patent as one of the things you could use for stress tests; right?

A. Correct. But stress testing --

Q. So it was well known that you could use TBHP for stress testing pharmaceutical active ingredients; right?

A. For stress testing, for example, for forced degradation studies, yes, it's used. But I was talking more about the stability product, the stability testing of the final product.

There's a big difference between those two things.

Q. Now, you're familiar with the FDA's stability testing guidelines; right, Doctor?

A. I'm familiar.

Q. And one of the FDA's recommendations for

drug product stability testing is 40 degrees Celsius, 75 percent relative humidity for six months; right?

A. Correct.

Q. And that's known as accelerated stability testing; right?

A. Correct.

Q. And it's standard practice to use accelerated stability testing; right?

A. To use accelerated stability testing, though, for the final product because that passage refers to finished final product.

Q. And it refers to finished final product because you're worried about the commercial use of the product; right?

A. Exactly.

Q. And you know that that test uses a higher temperature to accelerate the degradation that might occur; right?

A. Yes. It recommends that you can use a higher temperature, but not 60 -- you know, 60 degrees is pretty, pretty high. And also we need to make a note that the FDA guidelines refer to the finished product, not to a solution of

Rivastigmine, which is additional differences in the environment, which again, makes it impossible to extrapolate.

Q. The FDA does not provide any guidelines for determining the antioxidant effect of an excipient in a drug product; right?

A. For an oxidative degradation experiment, no, it doesn't. But, obviously, it provides guidelines for stability studies.

Q. Let me go back and ask the question again: The FDA does not provide any guidelines for determining the antioxidant effect of an excipient in a drug product; right?

A. No. Those are non-standardized tests.

Q. And Par's ANDA stability studies in the final product were not designed to answer the question of what the antioxidant effect of acetaldehyde was in the Rivastigmine product; right?

A. No, not really because the final testing of any pharmaceutical product, you know -- forget even the Par ANDA product -- is looking at the stability of that finished product.

So if there's something going on in

those final tests, they hope to pick it up. And as far as the materials that I saw, there was hardly any problems with any impurities there. The Rivastigmine specs were fine and it was substantially free of peroxides.

Q. Doctor, can you please turn to Page 176 of your deposition?

A. I'm there.

Q. Okay. So Dr. Kohn, look at Line 4. You were asked:

"Question: But I'm asking, are you suggesting that when Par designed these studies, one of the questions they were asking was what the antioxidant effect of -- of acetaldehyde was on Rivastigmine in their ANDA products?

"Answer: No, they were following FDA guidelines with a finished product that they hoped would reach, like every company, the specifications of keeping the amounts of the drug in the specifications. So they followed the guidelines. Obviously there is no FDA guidelines on what you are describing. These are the stability studies on the finished product."

Were you asked this question and did

you give that answer?

A. Yes. And it's the same answer I just said.

Q. So, let's go.

Now, FDA does not provide specific tests for conduct oxidative stress testing; right?

A. Correct. But does provide the final stability guidance.

Q. Okay. My question was stress testing. So let's limit the answer to my question.

You agree that the FDA does not provide specific tests for conducting oxidative stress testing?

A. So let's talk about stress testing --

Q. Doctor --

A. -- being a forced degradation study. We just need to define it.

Q. Okay. We can define that like this.

A. So forced degradation studies stress tests are not specifically guided by the FDA. Those initial tests that you do at the beginning before you do your research and development of a product, no, they're not standardized.

Q. And notwithstanding the lack of standard procedures, stress testing is routinely done in the pharmaceutical industry; right?

A. Yes. I would absolutely agree it has to be done.

Q. Okay. Now, Doctor, you criticized Dr. Davies for doing statistical analysis after his test was run; right?

A. Correct.

Q. And you did statistical analysis on his data after the test was run as well; right?

A. I did, but for the reason to show that he was incorrect in his methodology. But not to just -- I don't conduct tests after the -- after I'm finished with my design of experiments.

Q. And you testified that 0.05 is the only correct P-value that any scientist ever used. Did I understand you correctly?

A. No. What I said is that the scientific community regards P -- excuse me, P equals or lower than 0.05 between two test groups as being statistically significant.

Of course, you can see papers that look at P less than .0001, for example.

Q. Right. But let me restate the question.

So am I correct that you believe that having a P-value of 0.05 or less is the only correct way to determine whether something is statistically significant?

A. That is the scientifically reliable way that's accepted in the community.

Q. And 0.05 corresponds to a 95-percent confidence interval; right?

A. About.

MR. CONDE: May I approach, Your Honor?

THE COURT: Yes.

MR. CONDE: Can you please put up on the screen JTX 92, Mr. Hoy?

BY MR. CONDE:

Q. And could you please go to Page 101?

And could you please -- I'm sorry, page -- right there. There we go.

And could you highlight the right side on the upper left? There's an equation and then right below that equation, go to that full paragraph right there.

Yes. Okay.

And this is a reference that you cited in your report; right, Dr. Michniak-Kohn?

A. Yes, I did.

Q. Okay. And this is a discussion on what's referred to as confidence intervals; right?

A. Yes. It seems as though that's what they're discussing.

Q. And there's an equation for the confidence interval and then it says the confidence coefficient. That's the same thing as a confident interval; right?

A. Yes. I think it's a synonym for that.

Q. Okay. So the exhibit you rely on, DTX 92, says the confidence interval is a number related to the level of confidence we want. Typical values are 90, 95 and 99 with 95 being the most common.

Do you see that Dr. Michniak-Kohn?

A. Yes. I see that.

Q. So 90 percent is an acceptable confidence level; right?

A. With the proximate value --

Q. Ninety percent is accepted by this textbook that you relied on in your report;

right, Dr. Kohn?

A. Well, 95 being the most common.

Q. And 90 percent is also one of the typical values; right?

A. But most people wouldn't use that as being particularly strong at all.

Q. The textbook you relied on said 90 percent is a typical value that people rely on; right?

A. No. They just give a range of values that could be used. But, again, any peer-reviewed paper would look at P less than or equal to .05, which is approximately 95. But if you get a better value, you know, like a 99, then, obviously, that makes the statistics even stronger.

MR. CONDE: And, Mr. Hoy, could you please go to Plaintiff's PDX 144?

BY MR. CONDE:

Q. And I think you used this slide on your direct; right, Dr. Kohn? It's up on the screen?

A. Oh, yes. Yes, I did.

Q. And you don't dispute the confidence interval values that are on this slide that Dr. Davies calculated them correctly; right?

A. Well, apart from my initial calculation with proving that the one-tailed T test was not correct, I did not do anymore statistics because it's just improper to do this.

Q. This isn't statistics, this is taking the P value you said and converting it to a confidence level; right?

A. Well, what was your question exactly?

Q. So Dr. Davies took the P-values that he calculated and converted it to a confidence interval; right, a percentage?

A. Yes, he did.

Q. And you don't dispute his calculation of these confidence intervals based on the P values that were obtained?

A. As I have to mention that I did not go back and start doing all the recalculations on the statistics because I feel that that's a very scientifically unreliable way to go, so I did not do that.

Q. Dr. Michniak-Kohn, to say it's a 95 percent confidence interval means that you have a 95 percent confidence that the differences in the two values are real; right?

A. Yes, if it is an appropriate test in the first place.

Q. So doing the two-tailed T-test even under your analysis using unequal variants you would have an 87 percent confidence that the difference between Dr. Davies' values with acetaldehyde versus without acetaldehyde are real; right?

A. Well, I repeated the test and as we saw from my slide that all of those nine values weren't statistically significant.

Q. So let's go back to my question. So you'd agreed that even based on your statistical analysis, you can say that you have an at least 87 percent confidence that the difference between the data with acetaldehyde versus without acetaldehyde is real?

A. But I didn't do the exact conversion with the equation.

Q. Assume these conversions are correct, that tells us that you would have an 87 percent level of confidence that the difference between the data without acetaldehyde and with acetaldehyde is real; right?

A. Well, that makes the assumption that that

was correctly calculated.

Q. Now, on direct you talked about reaction kinetics; right?

A. Of course I did.

Q. And can we have the meaning of antioxidant on the screen again, Mr. Hoy, please.

Okay. So here is the meaning of antioxidant, PDX 105. The meaning of antioxidant doesn't make any mention of reaction kinetics, does it?

A. This particular sentence does not.

Q. And you testified about the restriction of movement on direct, and you did acknowledge that regardless of the fact that there might be some restriction of movement, antioxidants are used in formulations; right?

A. Well, in general in the pharmaceutical industry, antioxidants are used.

Q. Right. And they're used in tablets, for example; right?

A. They're used in tablets.

Q. And tablets have a restriction of movement as well; right?

A. Tablets have some restricted movement, I

agree. But again we haven't established the acetaldehyde as an antioxidant, so --

Q. And antioxidants, in fact, are used in Novartis's patch; right?

A. Antioxidants, yes, are used.

Q. And there would be a restriction of movement in Novartis's Exelon patch; right?

A. It is a transdermal patch.

Q. So there would be a restriction of movement with that patch as well; right?

A. Yes, there would be, but then you're working with particular antioxidants and we don't know whether acetaldehyde does that or not.

Q. So, Doctor, you did not do any statistical analysis of Par's stability data, did you?

A. No, I did not do any statistical analyses. I did see the data. It was pretty convincing and I don't think the FDA required any statistical analyses, either.

Q. So the answer is you didn't do any statistical analysis on Par's ANDA product to determine whether acetaldehyde present in those patches had an antioxidant effect; right?

A. Are you talking about the -- which

experiments are you talking about?

Q. You're familiar with Par's stability data?

A. Yes.

Q. Did you do any analysis of that data to see whether there was a statistical significant showing that acetaldehyde would or would not have an antioxidant effect?

A. No, I did not, because for two reasons, there the rivastigmine was within specs and the impurities were so low that some of those were zero, so you can't really do statistics on low values or not detectable values or zeros, so no, I did not.

Q. So because the values of degradants were so low, you couldn't do any statistical analysis on that data; right?

A. It certainly wasn't meaningfully so I didn't do that kind of data.

Q. Let's assume for the moment that you made two batches of Par's product, one patch had acetaldehyde and the other batch did not. Okay?

A. Okay.

Q. And then you put both of those batches, you put -- you put one patch from each batch and

you subjected to accelerated stability testing which would be 40 degrees celsius at 45 percent relative humidity. Are you with me?

A. I'm with you.

Q. At the end of six months you would take out of both of those patches and you would conduct HPLC to see how much degradant was in the two patches. Okay?

A. Okay.

Q. And the results of that show that the amount of rivastigmine was within specification and that the formation of Impurity 4 and ECAV were the same in both patches. Are you with me?

A. Okay.

Q. So based on that data from one patch from each batch, you would not be able to conclude that acetaldehyde has no effect on the oxidative degradation of rivastigmine; right?

A. Based on solely that data, no.

Q. And you would not be able to reach that conclusion because you won't be able to conduct good statistical analysis; right?

A. Not only that, but I would have done more studies. These would have been part of other

studies that would have been done in the industry.

Q. And that's because having taken only one patch is not sufficient to do statistical analysis; right?

A. Well, the FDA guidelines say that you can take one patch from a batch.

Q. That's not my question. My question is: The reason you can't reach the conclusion that acetaldehyde has no effect from my hypothetical because having taken only one batch does not allow you to do good statistical analysis; right?

A. You had a hypothetical case that you presented, which means that it's not a real case, it's a theoretical case. Nobody just takes one patch from two batches and runs data. In the pharmaceutical industry, you make batches all the time, so even if you take one batch and one transdermal patch from a batch, you're still testing numerous batches, so really it's not a true N equals one, it's much more than that.

Q. So let me just go back to my question. I just want an answer to my question. Based on my hypothetical would it be correct to say that you

would not be able to conduct good statistical analysis because you only took one patch from each batch?

A. Well, it follows FDA guidelines, but again, it's not -- your hypothetical is not real life, nobody just prepares two batches and then does one batch out of each. It's just not real life.

Q. Doctor, let's go to page 203 of your deposition. And let's go at line nine and starting at line nine, the question was:

"Can I conclude from that that my hypothesis is true, that acetaldehyde has no effect on oxidative degradation between lots zero and lots one?

And you know that in this hypothetical is the same one I just outlined, one lot had acetaldehyde and the other one did not; right?

A. Correct.

Q. Okay. And then you say:

"Did the rivastigmine content change in your two hypothetical batches?

"ANSWER: I mean if you were doing a

true stability test you would have also have your rivastigmine content.

"QUESTION: The rivastigmine content for both is within specification.

ANSWER: So again I would argue the same thing. The bleep is so small it could be within experimental error. I mean, you haven't done good statistics because we have only taken one patch and it's an N equals one. I don't think I would be making conclusions.

Were you asked that question and gave those answers?

A. Yes, I did, but I still state the same thing.

MR. CONDE: I have nothing further, Your Honor.

THE WITNESS: I said the same thing.

MR. CONDE: Nothing further.

THE COURT: Thank you.

Mr. Chin.

REDIRECT EXAMINATION

BY MR. CHIN:

Q. Dr. Michniak, I would like to follow-up on this hypothetical system. I believe Mr. Conde

had referred to it as lot zero and lot one?

A. Correct.

Q. Can you describe for me how that hypothetical situation of having lot zero and lot one compares to the 3M stability testing that was actually performed on the Par products?

A. It's a hypothetical because you would never do a series of tests on a batch and just do one out of each, and finish at that. The FDA recognizes that the pharmaceutical industries continually produce in different batches, so you can't use like half of your batch to do quality control of.

So they recognize that they're producing a lot of batches and it's enough to take one transdermal patch out of the whole lot of batches and then that is your number of replicates. You're producing all these batches and then you're able to do a real, real life perspective on what's happen with the patches.

In fact, it would be very bad to do the hypothetical case because what happens if a manufacturer changes your ingredients. You really have to test a whole series of batches and

I think the FDA just recognized that you can't take like fifty percent of each batch, you would be wasting it all on testing.

Q. Did the Par stability test perform tests on more batches than just a lot zero and a lot one?

A. Of course they did.

Q. I would like to turn back to JTX 92, we had that, actually we don't need to bring it up, but you recall that in JTX 92 Dawson Statistic textbook, there is a reference to a 90, 95 and 99 percent confidence?

A. I'm getting lost in my documents.

Q. If you can't find it readily, I can just ask the question in the abstract. You recall the discussion about a 90, 95 and 99 percent confidence intervals?

A. Yes.

Q. For what purpose -- and I think you had discussed with Mr. Conde that a 90 percent confidence interval roughly depending on the math translates to a P of 0.1?

A. Yes.

A. Yes.

Q. For what purpose would people use a confidence interval of 90 percent or P as .1?

A. Just to show a slight trend, but it wouldn't be relied upon to make scientific conclusions because, again, there's scientific literature that has accepted that P equal or less than 0.05 is your main kind of barrier. Because people put things below saying oh, it's much stronger statistically and "values above that".

But everyone knows that that's just the trend and you don't make major conclusions based on that.

Q. In the peer-reviewed literature, is there a definitive and clear cutoff for statistical significance that's recognized to be able to publish a scientific conclusion that's drawn?

A. Of course. It's what I've been saying the P equal to or less than .05. And I know that my papers would be rejected if I start making conclusions at higher P-values. You know, like with all mathematical calculations, you can calculate all kinds of P-values.

So the scientific community said, Well, where is the cutoff, the statistical

significance? And that's what they've decided. I mean, it's not my decision. It's science has decided.

Q. Now, there were also some questions that you were asked about articles that used TBHP in oxidative stress testing. Do you recall that?

A. Yes, I was.

Q. And I think you point out that that's also known as forced degradation?

A. Correct.

Q. Can you describe for me the purpose for which TBHP is used in these forced degradation tests?

A. So that's why I brought up the term forced degradation studies because those kind of studies are done across the industry. They're not standardized in the sense that the FDA has mandated that this is what you have to do.

And they're done right upfront before you even start your research and development. For example, learn about the drug and, you know, if you stress test it, if we're using the forced degradation study as stress testing, stress test under extreme conditions

because that gives -- you have all the chemical information on how you start preparing a dosage form.

If you don't know that, you don't know whether you can expose your drug to heat, for example, what's going to happen. Then you have to have the reaction take place fast, get enough of your degradation products to be able to test as you do your research and development, whether those degradation products are appearing.

And you have to have enough of them. So you do these forced degradation studies for those reasons to learn about the chemistry of the active ingredient or excipients by the way -- that goes into the dosage form and also to get enough of the substance to be able to use it as a standard for your further analytical testing.

So there's, obviously, a role and very important role for forced degradation studies in the industry.

Q. Do people in the pharmaceutical industry use these forced degradation oxidative stress tests to determine the stability of finished pharmaceutical products?

A. No, these tests are, as I just mentioned, done upfront before you start developing or during your development of your pharmaceutical dosage form. But the FDA tells us what needs to be done to evaluate stability of a finished product.

And those two are very different.

MR. CHIN: Thank you.

MR. CONDE: Your Honor, may I have one more minute, please? A recross?

THE COURT: No, I understand what you're asking for. Did Mr. Chin ask something that was beyond the scope of what was brought up in your cross-examination?

MR. CONDE: She started to go into more details of what Par actually does about testing the patches and it's clearly not correct. So I wanted to --

THE COURT: All right. So, no, you can't do anymore.

Doctor, I do have one question. Say in the last five years, how many times have you testified in Court as an expert?

THE WITNESS: In Court? I'd have to

admit to the Court that this is my first time.

THE COURT: Well, everybody starts with a first time.

THE WITNESS: Yes.

THE COURT: Thank you.

THE WITNESS: Thank you, Your Honor.

THE COURT: Mr. Chin.

MR. CHIN: Your Honor, Par calls Dr. Graham Buckton.

THE COURT: All right.

THE CLERK: Please state and spell your full name for the record.

THE WITNESS: My name is Graham Buckton. That's G-R-A-H-A-M B-U-C-K-T-O-N.

THE CLERK: Please place your left hand on the Bible and raise your right hand.

GRAHAM BUCKTON, Ph.D.,.

the witness herein, having first been duly sworn on oath, was examined and testified as follows:

THE CLERK: Thank you. Please be seated.

MS. KOH: Your Honor, may I approach?

THE COURT: Yes.

DIRECT EXAMINATION

BY MS. KOH:

Q. Good morning.

A. Good morning.

Q. Could you please state your full name?

A. It's Graham Buckton.

Q. Could you please briefly describe your relevant employment?

A. Yes. I'm employed 30 percent of my time at the University College of London, School of Pharmacy as professor of pharmaceutics. And 70 percent of my time in Buckton Consulting.

I was previously -- I was founder and chairman and chief executive officer of Pharmaterials from 2000 to 2012.

And I also worked with U.K. Regulatory Committees from 2004 until now. U.K. Regulatory Committees, which unlike the FDA, the U.K. has a scheme where expert committees look at the assessments that are being made of new products and decide whether they should receive a marketing authorization.

So, each month I would receive five

or ten regulatory submissions.

Q. And you mentioned your involvement with Pharmaterials. What is Pharmaterials?

A. Pharmaterials was a company that spun out of a school of pharmacy in London, which I founded. And it provides service to industrial companies, and in terms of materials, characterization, formulation, manufacturing, analytical development and stability testing.

Q. And have you served as an editor or on an editorial board for peer-reviewed journals?

A. Yes, I was an editor of International Journal of Pharmaceutics for ten years. I served on a number of editorial boards, including Pharmaceutical Research, AAPS Journal and AAPS PharmSciTech.

And I served on the Steering Committee of the Handbook for Pharmaceutical Excipients.

Q. You mentioned the Handbook of Pharmaceutical Excipients. What is the handbook?

A. The handbook is a comprehensive listing of the excipients that are used in pharmaceutical products.

Q. And you mentioned you're on the Steering Committee for the handbook. What does the Steering Committee do?

A. Steering committee meets twice each year to review the monographs to review the excipients that are going to be included into the handbook and to decide whether the monographs are correct and reasonable.

Q. Could you please turn to Tab 1 in your binder, which is DTX 503A?

Could you please identify this document?

A. That's my CV.

Q. Does this CV at DTX 503A accurately reflect your background and experience?

A. To the best of my knowledge, it does, yes.

MS. KOH: Par moves for the admission of DTX 503A into evidence.

MR. CONDE: No objection.

THE COURT: All right. Admitted without objection.

MS. KOH: Par offers Dr. Buckton as an expert on drug substance testing, formulation development and stability testing of

pharmaceutical products.

MR. CONDE: No objection, Your Honor.

THE COURT: All right. You may proceed.

BY MS. KOH:

Q. Dr. Buckton, which party retained you to testify as an expert in this case?

A. That was Par.

Q. And what has Par retained you to do?

A. To review the relevant documents and to give an opinion on whether Par's ANDA product infringes the claims of the patents and also to comment on the validity of the patent.

Q. Have you been in the courtroom throughout trial so far?

A. Yes, I have.

Q. And have you heard all the fact and expert testimony that has been presented to date?

A. Yes, I have.

Q. And have you considered that testimony in offering your opinions today?

A. Yes, I have.

MR. CONDE: Your Honor, I don't mean

to interrupt, but we had an agreement, I think, that Professor Buckton's going to do his infringement portion and then make a clean break and then do his invalidity portion, so that we have a sense as to what his invalidity arguments are. As you may recall, at the pretrial conference, it was discussed about this.

THE COURT: That's what I thought I said at the end of yesterday. That makes me think that's not what we're doing.

Are we doing something different?

MS. KOH: We can do something different.

MR. CONDE: I just want to be clear on that.

THE COURT: Even though, I have to say, you know, I was thinking about it last night afterwards and it's not as though he says something now and when invalidity comes up, you know, if you say, Well, geeh, he said that during the infringement portion. I'm going to say, Oh, okay. It doesn't count.

I mean, so I'm not actually -- only because I said that this is the way we'd do it

last night, the more I thought about it, I'm not actually sure it makes any sense. But, in any event, Ms. Koh, if you're able to do it like that, it would be good. Okay?

MS. KOH: We will do that. Sure.

BY MS. KOH:

Q. Dr. Buckton, what is your opinion on whether Par's ANDA products infringe the '031 patent?

A. My opinion is they don't infringe.

Q. And do you have a summary of your reasons why?

A. Yes, I do. I have a slide for that.

My summary that Par does not infringe the '031 patent because Par's ANDA products do not contain an antioxidant. The evidence does not establish that acetaldehyde is an antioxidant.

Acetaldehyde is not present in Par's ANDA products in the claimed range of about 0.01 to about 0.5 percent by weight.

And the amount of acetaldehyde in Par's ANDA products does not meet the about limitation because it does not function to

stabilize Rivastigmine in the composition.

Q. Could you please turn to Tab 2 which is JTX 1 in your binder? What is this document?

A. It's the '031 patent.

Q. And have you reviewed the '031 patent?

A. Yes, I have.

Q. Do you have an understanding of what claim plaintiffs are asserting that Par infringes?

A. Yes, I do. It's -- I have a slide with the claim on it.

Claim 7, as I think you've seen, Claim 7 incorporates Claim 1 as part of it.

Q. Well, what does Claim 7 require?

A. Claim 7 requires a transdermal device and it's a pharmaceutical composition. And, among other things, Claim 7 requires that there is an about 0.01 to about 0.5 percent by weight of an antioxidant present based on the weight of the composition.

Q. Do you understand that the Court has provided a construction of the terms used in Claim 7?

A. Yes, I do.

Q. And have you reviewed the Claim

Construction Order?

A. Yes, I have.

Q. And have you applied the Court's claim construction in your analysis in this case?

A. Yes, I have.

Q. So going back to the '031 patent, can you tell the Court what the patent describes?

A. Yes. I've also prepared a slide for this. The patent has three aspects that it talks about.

The first aspect, it says a pharmaceutical composition comprising Compound A in free base or salt form and an antioxidant. And it says the pharmaceutical compositions of the present invention show a reduction in degradation by products in stress stability tests. That's the first aspect.

The second -- that was on Column 1, Lines 34 to 39. The second aspect at Column 4 at Lines 4 to 7 says, in another aspect, the present invention provides the use of an antioxidant to stabilize a pharmaceutical composition containing Compound A. Compound A is Rivastigmine.

And then the third aspect, which is found in Column 4, Lines 33 to 39 largely

describes a transdermal device and aspects relating to a transdermal device which you would administer Compound A.

Q. Is there any difference between these three aspects?

A. I think the third one, as I just said, describes the device, aspect one and aspect two. To me, there are no differences between because they require a pharmaceutical composition of Compound A, and they require an antioxidant and they require that you show a reduction in degradation by-products by stress stability tests. And then that seems to me to relate to both of those aspects.

Q. How did the patent describe the use of an antioxidant to stabilize compound A to reduce degradation by-products?

A. I have a slide for this as well. The patent at column four lines 20 to 30 describes two tests, the first test I summarize both of them in the table so the first test is a 60 degree centigrade for two months. And the patent looks at a formulation, pharmaceutical formulation in which there is no antioxidant and

compares it to a pharmaceutical formulation in which there is 0.1 alpha-tocopherol as an antioxidant and the degradation products are 4.46 percent where there is no antioxidant present and 1.3 percent when the alpha-tocopherol antioxidant is there.

And I follow this up with a further test at 40 degrees C, 75 percent relative humidity for a period of three months and again I compare a formulation with no antioxidant to a formulation with 0.15 percent antioxidant which is alpha-tocopherol with a degradation is 1.19 to 0.25 percent.

Q. What's the approximate reduction in degradation of by-products after an antioxidant was added?

A. Roughly speaking for both of those it's about a quarter.

Q. And is the approach described at column four, lines 20 through 30 of the '031 patent used in the pharmaceutical industry?

A. Yes, this is typical of what I have seen in the pharmaceutical industry that you have perhaps a rapid stress test looking at a

formulation at 60 degrees C for a short period of time to give you a rapid indication of what happens, followed up by a stress which is rather near to room temperature in line with regulatory guidelines which is 40 degrees centigrade and 75 percent relative humidity and ultimately you would progress to ambient storage, that's where you would go. But this is exactly what I would expect the industry to do.

Q. Does the '031 patent specification indicate the concentration range for antioxidant in the composition?

A. Yes, it does. And we have a look at a slide for this. This is column four, lines 15 to 17. At the start of that it says the antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5 percent.

Q. And does the '031 patent specification describe any examples of the use of an antioxidant outside of the range of about 0.01 to about 0.5 percent?

A. No, it doesn't. There are two examples that I just talked about a few moments ago, and this continues on to use those concentrations one

of those examples, 0.15 percent and the other example used 0.1 percent so those are the two examples in the patent.

Q. Did you consider any other information as to what the claimed range encompasses?

A. Yes, I did. I looked at the file prosecution history.

Q. Could you please turn to tab three in your binder which is DTX 249. Could you please identify this document?

A. This is a section of that file prosecution history.

MS. KOH: Par moves the admission of DTX 249.

MR. CONDE: No objection.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. If you can turn to page 1078 of DTX 249. Does the prosecution history of the '031 patent indicate the purpose of the range limitation?

A. Yes, I believe it does. The first section of that I pulled out here on the slide says that the examiner also rejected the claims on the

basis that the specification does not enable the use of any amount of antioxidant in the composition to achieve the stabilization of compound A. At that stage there was no range limitation, there was no concentration term in what has now become Claim 1 of the '031 patent.

And the examiner continued saying that that isn't viable because there are no data to enable any amount of antioxidant, and the response to that was to include the range limitation of about 0.01 to about 0.5 percent by weight in order to enable the patent.

Q. Does the prosecution history indicate what about in the range limitation means?

A. Yes, it does. And it says here that given the use of about in the claim, applicants do not surrender embodiments where an infringer copies the invention by using amounts outside of the exact claimed numeric range. Skip a little bit, more specifically, where an infringer uses some excess of antioxidant needed for stabilization.

So it's clear to me from the statement that they're envisioning a situation where there is an antioxidant functioning within

the claimed range, and it clearly would be wrong if someone just added a small excess of that antioxidant in order to still function but be outside of the claimed range. That would seem inappropriate.

So I understand why the applicants wanted to protect particularly in excess of antioxidant needed for stabilization. There is no similar argument below the claimed range, so about in terms of its meaning below the claimed range isn't given that kind of explanation, and that is the reason that wasn't deemed to be enabled in the previous section that I read out. So I don't see such a clear reason for deviating below the claimed range.

Q. Does the range limitation include amounts that are capable of functioning but have not been shown to function as an antioxidant in the composition?

A. No. The file history talks about functionality, and the need to function. It doesn't describe an antioxidant that may be capable of functioning, capable of functioning would imply not functioning, something either is

or it isn't functioning.

Q. Going back to your summary of noninfringement opinion, what is your first noninfringement opinion?

A. My first opinion is that Par does not infringe the '031 patent because Par's ANDA products do not contain an antioxidant.

Q. Now, there has been some discussion about Par's ANDA products already, but could you please describe what are Par's ANDA products at issue?

A. Par's ANDA products are three different versions of a transdermal delivery system.

Q. Could you please describe briefly for the Court the structure of Par's ANDA product?

A. I think, yes, I can. We have seen this, it's a drug-in-adhesive matrix. On top of it is a backing layer, on bottom of it is a release liner which is removed just before you apply it to the skin.

Q. Could you turn to tab four of your binder which is DTX 595. Could you please describe what this document is?

A. This is the quality overall summary of Par's ANDA.

MS. KOH: Par moves the admission of DTX 595 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. If you could please turn to page 231 from DTX 595. Could you please explain what the table on this page shows.

A. Yes. The table is the components composition and function of the components. And to simplify it, I have put a slide on the screen which describes the three different strengths of Par's ANDA products, the 4.6 milligram and the 9.5 and the 13.3 milligram strengths. They all consist of rivastigmine as an active ingredient. They all consist of acetate copolymer adhesive, that's the R-27149 and they all consist of isopropyl myristate as a tackifier, and those add up to a hundred percent of what is called the drug in adhesive.

They also have two films, Scotchpak 9732 backing film and Scotchpak 9744 release

liner.

Q. Could you please turn to page 232 of the same document. Could you please explain what this page shows, the chart at the bottom?

A. The chart at the bottom. Okay. So this is a chart going over two pages which I have reproduced here. And this compares the Exelon patch and its ingredients to the proposed Par ANDA transdermal system. And in particular what I wanted to highlight was the Exelon patch has vitamin E present which is an antioxidant, and the proposed Par product has N/A, not applicable, because it doesn't have an antioxidant as part of its formulation.

Q. And is vitamin E tocopherol?

A. It is.

Q. Can you explain why an antioxidant may be needed in the one formulation but not in another formulation of the same active ingredient?

A. Yes. It's different formulations have different properties and different reasons why something may react in one and not react in the other. So it's to do with the formulation.

Q. Could you please turn to tab six which is

JTX 71 in your binder. What is this document?

A. This is the pharmaceutical development part of Par's ANDA.

MS. KOH: Par moves the admission of JTX 71 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. Could you please turn to page 1071 of JTX 71. Did Par or 3M address oxidative degradation when developing Par's ANDA product?

A. Yes, they did. And this section just before we get to section 4.1 which is highlighted on the screen, it says since 3M designs and prepares adhesives internally, the opportunity to purify our adhesives allows for minimization of adhesive impurities that may contribute to drug degradation. The primary pathway pursued by 3M was to formulate without an antioxidant.

Q. And how did 3M minimize the adhesive impurities that might contribute to drug degradation?

[redacted]

Q. Did 3M test the stability of formulations using the adhesive?

A. Yes, it did.

Q. Could you please turn to page ACR-1088 of JTX 71. What do these pages show?

A. This talks about the stability test and

the section at the top and the results, I don't know if they can pull out a little bit. To evaluate the stability of rivastigmine in an adhesive only DIA formulation, a representative DIA formulation was prepared and placed on informal stability under ambient and accelerated conditions, 25 degrees C, 60 percent relative humidity and the accelerated condition was 40 degrees C and 75 percent relative humidity. And it says the results of the informal stability six-month pull point says that the use of antioxidant is not indicated to stabilize rivastigmine in R-27149 adhesive based formulations.

Q. Does this statement that you just read from page 1088 of JTX 71 referring to instability studies, does it relate to Par's ANDA products at all?

A. It does relate to them. This is the polymer and rivastigmine only system , so there is no tackifier present, so it isn't the absolute final formulation, so it wasn't exactly Par's ANDA product, but it would relate to what happened in Par's ANDA product.

Q. Based on your review of Par's ANDA, do Par's ANDA products contain an antioxidant?

A. No, they don't.

Q. Could you turn back to your summary of opinions. What is your second opinion?

A. My second opinion is the evidence does not establish that acetaldehyde is an antioxidant.

Q. Now, do you agree with Dr. Davies that acetaldehyde is an antioxidant?

A. No, I don't.

Q. And what are your reasons?

A. I have a slide for this. Acetaldehyde is not an antioxidant. Firstly because acetaldehyde is not listed in the '031 patent as an antioxidant. Secondly, because it is not listed in the Handbook of Pharmaceutical Excipients or other pharmaceutical literature as an antioxidant. And thirdly because acetaldehyde has never been used as and is not recognized as an antioxidant. And finally, the stability data show that acetaldehyde has no effect on the stability of rivastigmine.

Q. Could you please explain your first reason why acetaldehyde is not an antioxidant?

A. The first reason it simply is not listed in the '031 patent as an antioxidant.

Q. Could you please go into that further?

A. Yes. This is the section from the patent which describes column four lines 10 to 15, the antioxidants, and it says effective stabilizing effect is surprisingly achieved when the antioxidant is selected from tocopherol, esters thereof, e.g., tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, or propyl gallate, preferably alpha-tocopherol or ascorbyl palmitate.

Those are the antioxidants that you should select from, from the words that are used in the patent.

Q. Are any of the antioxidants listed in column four, lines 10 through 15 not generally known to be antioxidants?

A. No, all of these are well known pharmaceutical antioxidants which are seen in standard pharmaceutical texts.

Q. Could you please explain your second reason why acetaldehyde is not an antioxidant?

A. The second reason is that acetaldehyde is not listed in the Handbook of Pharmaceutical Excipients or other pharmaceutical literature as an antioxidant.

Q. Could you turn to tab eight which is DTX 505 in your binder. What is this document?

A. This is an excerpt from the Handbook of Pharmaceutical Excipients.

MS. KOH: Par moves the admission of DTX 505 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. Does the Handbook of Pharmaceutical Excipients list antioxidants?

A. Yes, it does. The part of the index is on page 857, and it lists antioxidants, and it lists a long list of antioxidants in that section. And acetaldehyde is obviously not listed in that list of antioxidants which are the ones that are known in the pharmaceutical domain.

Q. Is acetaldehyde identified anywhere else

in the Handbook of Pharmaceutical Excipients?

A. No, it isn't listed anywhere in the Handbook of Pharmaceutical Excipients so it's not listed as any other type of excipient either, so it's nowhere else.

Q. Is acetaldehyde identified in any other pharmaceutical literature as an antioxidant?

A. Not that I'm aware of, no.

Q. Going back to your summary, could you please explain your third reason why acetaldehyde is not an antioxidant?

A. The third reason is acetaldehyde has never been used and is not recognized as an antioxidant.

Q. Is there a source to turn to find a list of excipients that have previously been used in pharmaceutical products?

A. Yes, there is. There is the FDA inactive ingredient list.

Q. Is acetaldehyde listed on the FDA inactive ingredient list as an excipient that has been used in a pharmaceutical?

A. No, it has not. I have a screen shot, if you type in acetaldehyde, it comes back with no

records matched your search. Which means that in none of the products that the FDA has licensed is acetaldehyde present in any form, never mind as an antioxidant, it's not present as an excipient in any of them.

Q. Would a person of ordinary skill in the art recognize acetaldehyde as an excipient?

A. No, they won't.

Q. Could you please explain your fourth reason why acetaldehyde is not an antioxidant?

A. The fourth reason is the stability data shows that acetaldehyde has no effect on the stability of rivastigmine.

Q. What are methods for testing stability of a drug product?

A. Methods for testing stability are long-term storage, that's the gold standard if you like. You store a product at ambient conditions for its shelf life, and that's as good as you can do, that's the true stability of the drug product. And then there are accelerated conditions that you can use because if you have a two-year shelf life you can't reasonably wait two

years to find out whether your first formulation is stable or not, so you have accelerated conditions that you can use to get data rather quicker.

Q. Are there

Q. Are there standards for conducting accelerated and long-term stability testing?

A. Yes. For example, there are FDA standards.

Q. Would you please turn to Tab 9, DTX 591 in your binder? What is this document?

A. This is the FDA standard for stability testing of new drug substance and products.

MS. KOH: Par moves the admission of DTX 591 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. Could you please turn to Page 7 of DTX 591? What does this page show?

A. The section of the bottom of this and straddling over to the next page, it gives the

standard conditions that the FDA have for storing a drug product for stability. And first one is long-term testing.

And long-term testing is room temperature testing. And as I said, that's the absolute gold standard, as it were.

And that's 25 degrees C, 60 percent relative humidity for a relative period of 12 months, carrying onto the full shelf life of the product.

And intermediate testing is, obviously, slightly accelerated 30 degrees Centigrade and 60 percent relative humidity for a period of 12 months. And the accelerated condition, which obviously is more stressed data.

Accelerated test is 40 degrees C, 75 percent relative humidity for a period of six months.

Q. Can accelerated or long-term stability testing be used to show whether an antioxidant is needed in a formulation?

A. Yes, they can. So if you were to make a formulation and store it on accelerated or long-term stability, if it were unstable, you

would be able to observe that in your study and you would be able to test by including an antioxidant and see if it would stabilize it and see if it would function.

Q. Can accelerated or long-term stability testing be used to show whether a compound is acting as an antioxidant?

A. Yes, it can. As I just said, if you make a pharmaceutical composition with and without the compound as in the patent where there's a formulation without and a formulation with an antioxidant, you can compare them and see if it's active.

Q. Are there any other sources that describe testing to determine whether a compound is acting as an antioxidant?

A. Yes. There are -- there European guidelines, EMEA guidelines, also.

Q. Could you please turn to Tab 10 in your binder, JTX 105? And what is this document?

A. This is a Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products.

Q. This is the EMEA document?

A. This is the EMEA document, which is the European kind of equivalent of the FDA.

Q. And could you please turn to Page 2 of JTX 105? And what does this page say?

A. If I would be able to call out the top paragraph, just that's about right. Yes.

The efficacy of antioxidants must be assessed in the finished product in conditions which simulate actual use by measuring the extent of degradation in the finished product with and without the antioxidant.

So that the first paragraph there is very clear that it's necessary to understand the workings of an antioxidant within the context of a pharmaceutical formulation and to test it within a pharmaceutical formulation.

And the second paragraph is important, too. It says that antioxidants should only be included in a formulation if it has been proved that their use cannot be avoided.

So it's not something you would go to as the first thing you would consider. And it says that you should regularly look at

manufacturing process and optimize those to minimize the potential for oxidation.

In line with where we are, the Par product where the formulation and the manufacturing process is being optimized to avoid the need for using an antioxidant.

Q. Does the method described in the EMEA guidelines that you just described relate to the methods in the '031 patent?

A. Yes, it does. As it says with EMEA guidelines you just heard, you should do your formulations with and without an antioxidant present to establish whether the antioxidant is functioning in that product.

So the guidelines are in line with how the test was run in the '031 patent.

Q. What is your conclusion as to what are these standard tests for determining whether a compound is an antioxidant?

A. Standard test is to take a formulation with and without an antioxidant and to stress them initially at a rapid high temperature like 60 degrees, which was used in the patent, and then subsequently following it up at conditions

in line with the regulatory conditions, such as 40 degrees Centigrade and 75 percent relative humidity, which was used in the patent.

And, ultimately, if you're going to use that, you would carry on to long-term use storage, 25 degrees C, as the FDA would require. So that's it as it would go down.

Q. And what is your support that accelerated stability tests are the standard test for determining whether a compound is an antioxidant?

A. Accelerated stability testing in the formulation, is what's described in the '031 patent and is what's described in the FDA guidelines. And it's what's described in the EMEA guidelines.

So that's my support.

Q. Have you seen any accelerated stability testing data relevant to the question of whether acetaldehyde is an antioxidant?

A. Yes. I've seen stability testing data on the Par product.

Q. Let's talk about Par's ANDA products. Were acetaldehyde levels measured in batches of Par's ANDA product?

A. Yes, they were.

Q. And could you please go through those?

A. So measured -- this is a table of different batches of Par's ANDA product. The first line is lot 110110, 4.6-milligram patch and tested three repeat tests.

It's not detected. So it's not a detectable amount three times. And I think a reasonable conclusion from that is that there's none present.

So I put that as a mean of zero parts per million on the basis that it's not detectable by those methods.

The next line is 110111 9.5-milligram patch. Again, there was no acetaldehyde detected. So I put that as a mean of zero parts per million of acetaldehyde.

The next one is 110280 9.5-milligram patch, tested three times, 13, 13 and 14 parts per million. And that's a mean of 13 parts per million.

And 110281 of 4.6-milligram patch tested at 14, 16 and 15 parts per million. So that's a mean of 15 parts per million.

And 110319 is the 9.5-milligram

patch tested at 13, 13 and 10 parts per million. That's a mean of 12 parts per million.

The next one -- excuse me. The next one is 110320 4.6-milligram patch and it was tested at 11, 8 and 12 parts per million. So that's a mean of ten parts per million.

The next one is 130108, 13.3-milligam patch, tested 30, 25 and 21 parts per million, which is a mean of 25 parts per million.

The last one is 130140 -- sorry, 130141, which is a 13.3-milligram patch, which was tested at 25, 26 and 23 parts per million. And a mean of 25 parts per million.

So, for me, the not detected takes this from a range of zero to the largest single number was 30 parts per million. And the mean range from, I would say, zero not detected certainly up to 25 parts per million.

And in terms of a percentage in the formulation, that's from nothing up to 0.0025 in the formulation.

Q. Could you please turn to Tab 11 in your binder, please which is DTX 585B.

Does this document provide the acetaldehyde measured in the table you just presented?

A. Yes, it does.

MS. KOH: Par moves the admission of DTX 585B into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. And the sources at the bottom of DTX 585B include JTX 180, JTX 181, JTX 169, JTX 197, JTX 198, JTX 199, DTX 617 and DTX 618.

Has Par run stability tests on the ANDA product for which it measured acetaldehyde levels?

A. Yes, it has.

Q. And could you please walk us through that data?

A. Sure. These data are the summary of the stability testing data at 25 degrees C and 60 percent relative humidity, which are the long-term stability data. As I said, these are

the gold standard that you look to.

And they take us out all the way to shelf life of the products. So the top two rows here in yellow take us from batch 110110 from initial all the way out to 24 months.

And these are the oxidative degradation breakdown products, Impurity 4 and ECAV for that two-year period. And the other highlighted in yellow is 110111 and that goes all the way out to 24 months. So the top two rows of this show that if you have zero for not detected or zero, as I would say, acetaldehyde in those two batches, there was no degradation at all. It would be measured over the entire shelf life of Par's ANDA product.

And for me, if you have no detection of any oxidative degradation products in the data, that the absolute room temperature data for the whole shelf life of the product, there's no way that situation can be improved by the inclusion of acetaldehyde.

It's as stable as it can possibly be. If you look at the other data on here, the one that's grayed out is 110177. And for this

batch, there was no measurement of acetaldehyde so this is grayed out because I don't know whether it contains any acetaldehyde or not.

It's an unknown in that respect. That was entirely stable through the entire two-year shelf life, too. And the other batches going down here are the various batches for which acetaldehyde has been measured and detected.

And we just talked about those a few moments ago. A few of them don't go out to the full shelf life because there hasn't been long enough storage yet to take them out the 24-month time period. So they only have nine months available so far.

But I would say all of these data demonstrate a remarkable stable product, which is showing no meaningful evidence of oxidative degradation and absolutely no evidence at all that acetaldehyde can reduce oxidative degradation because the product is clearly stable without any need for it.

And I've then also put data of the accelerated conditions. So the next slide is 30 degrees C and 65 percent relative humidity. And

again, the first two rows are the ones with zero acetaldehyde. And they are both accelerated stability studies stability testing and they're both remarkably stable.

There is nothing at all to be talked about. 0.1 I wouldn't say was any great meaning.

And it reverts to less than 0.1 on the last time point. So there's no degradation to talk about in the first one.

It's a very modest hint of degradation. At the very end, that's a very stable compound and very stable formulation or very stable formulation rather.

If you look at the other dates on there, there are incidences here and there of a measured amount of degradation. But the story of this slide is very clearly one of a stable formulation and one that I can see no evidence whatsoever that acetaldehyde is reducing any degradation.

There's nothing to support that, in my view. The data are very clean, very clear and it's a stable product for which there can be no reduction really in degradation by acetaldehyde.

And the final data says 40 degrees C and 75 percent relative humidity and this is the most stress, the most accelerated condition. And inevitably, in this condition, there will be more degradation for compounds which is liable to oxidative degradation.

We know that is the case. So inevitably numbers at the end of this will start to develop. This column here will start to show some measurable numbers for degradation.

But the story here is very much the same. Throughout the storage, these materials are stable. They never go out of specification.

I see no evidence even in this stress condition. I see no evidence of acetaldehyde protecting against oxidative degradation. And I would stress the most important data we would consider are real-time storage.

These are not least important because these are the ones you use to get your first indication of what's happening. But they're -- the really important ones are the real-time storage. Each of the three conditions,

I see no evidence at all for any reduction in degradation of Rivastigmine in this composition by the presence of acetaldehyde.

Q. Dr. Buckton, if you could please turn to Tab 12 in your binder, which is DTX 588B. Does DTX 588B provide the stability data for the 25 degrees, 60 percent RH condition that you just discussed?

A. Yes, it does.

MS. KOH: Par moves the admission of DTX 588B into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: All right. Admitted without objection.

BY MS. KOH:

Q. And could you please turn to Tab 12A and 12 -- 12A which is DTX 578 and Tab 12B, which is DTX 600. And do those documents provide the raw data for the stability testing data you just presented?

A. I think that's right.

MS. KOH: Par moves for the admission of DTX 578 and DTX 600 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. And can you please turn to Tab 13 in your binder, Dr. Buckton, which is DTX 587B and does DTX 587B provide stability testing data that you presented for the 30 degrees 65 RH data that you just discussed?

A. That's correct.

Q. And could you please turn to Tab 13A in your binder, which is JTX 193? And does JTX 193 provide the raw data underlying the stability testing data in DTX 587B?

A. Say that again, please.

Q. Sure. Does JTX 193 provide the raw data underlying the stability testing data in DTX 587B?

A. What was the tab again?

Q. Sorry. 13A. Tab 13A.

A. I'm sorry, yes. It does.

Thank you.

MS. KOH: Par moves for the

admission of JTX 193 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. And if you could please turn to Tab 14 in your binder which is DTX 586B. Does DTX 586B provide stability data for the 40, 75 condition that you just discussed?

A. Yes, it does.

Q. And if you could please turn to Tab 14A, which is JTX 200, Tab 14B, which is PTX 140, Tab 14C, which is PTX 138, and Tab 14D, which is PTX 141?

And do those documents JTX 200, PTX 140, PTX 138 and PTX 141 provide the raw data for the underlying stability testing data in DTX 586B?

A. I think they do. Yes.

MS. KOH: Par moves for the admission of JTX 200, PTX 140, PTX 138, and PTX 141 into evidence.

MR. CONDE: No objection, Your

Honor.

THE COURT: Admitted without objection.

BY MS. KOH:

Q. Dr. Buckton, are the stability testing data for Par's ANDA products reliable?

A. Yes, they're reliable. They're stability testing data generated by validated methods and submitted to the FDA. So, yes, they are.

Q. And what is the specification for the degradation products ECAV and Impurity 4 in Par's ANDA product?

A. The specification is 0.5 percent for each of them. So each of them individually 0.5 percent.

Q. And is this a not more than 0. --

A. I apologize. That's not more than 0.5 percent.

Q. What is your conclusion based on the accelerated and long-term stability data as to whether acetaldehyde is an antioxidant?

A. I see no support for that it's an antioxidant and I don't see any reduction in oxidative degradation of Rivastigmine in the

presence of acetaldehyde.

Q. Dr. Buckton, do you believe that the accelerated and long-term stability tests for Par's ANDA product were set up for the express purpose to see whether or not acetaldehyde was an antioxidant?

A. No. I don't believe that's why they were set up.

Q. And why not?

A. I don't think that's what anyone would do. I don't think anyone would view acetaldehyde as an antioxidant, so I don't think you would set up tests for that purpose. You would set up to look at the stability testing of their product.

Q. If the accelerated and long-term stability testing tests are not set up for the purpose of evaluating acetaldehyde as an antioxidant, do those tests still allow you to draw that conclusion?

A. Yes. I believe they do. The experimental design allows you to have batches with acetaldehyde and batches without acetaldehyde in pharmaceutical formulations. So I think it allows you to draw those conclusions.

Q. Did you hear Dr. Davies' criticism that you improperly compared Par's ANDA batches because they were made from different lots of ingredients?

A. Yes. I heard that criticism.

Q. And what's your response to that criticism?

A. I don't think it's valid for a few reasons, firstly the regulatory authorities actually want you to do that, it's a good thing to do. If you can demonstrate that a product is uniformly stable with a wide range of lots and different batches, it's very good evidence that you have a product which is uniformly stable rather than a freak observation with one off response, for example.

So it's a good thing. And I think the data is internally consistent so it's a coherent data set all of which demonstrate stability and all of which can be relied upon to support the same overall view.

Q. Can we return to your summary of noninfringement positions. Can you please explain your third reason why Par's ANDA products

do not infringe Claim 7?

A. The reason is acetaldehyde is not present in Par's ANDA products in the claimed range of about 0.01 to about 0.5 percent by weight.

Q. Is there any purpose for acetaldehyde in Par's ANDA products?

A. No, there isn't. It's there as a residual solvent, it isn't there for any purpose, if it's there at all. Actually there are some batches, I don't think it's there at all.

Q. Could you briefly explain what is a residual solvent?

A. Residual solvent is a volatile organic material which is either used during the manufacture of an API or excipient or formulation or generated during the manufacture of an API or excipient.

Q. What levels of residual solvents should a drug product contain?

A. It should be as low as you can possible manage, it's not there to have any function, they're not generally desirable things, so you should minimize it or remove it would be your goals.

Q. Is a residual solvent the same as a pharmaceutical excipient?

A. They're very different. A pharmaceutical excipient is there for a particular reason, a residual solvent is not. I have a slide which compares those things. A residual solvent doesn't have a functional purpose. It's there as an unfortunate consequence and something you don't want to have present. An excipient is there for a functional purpose, you have it there for a deliberate intent to achieve something in the formulation.

A residual solvent is not there at a set concentration. The goal is to remove it and not have it present. Whereas to achieve a functional purpose, an excipient must be there in a certain amount and it will have a defined amount in the pharmaceutical formulation.

A residual solvent will have a not more than specification, and the desire to keep it low or preferably eliminate it entirely from the formulation whereas that is not the case with an excipient which will be there at a set concentration or a particular functional purpose

for which it is being investigated to perform.

Q. Does Par's ANDA include a specification for an amount of antioxidant in the final pharmaceutical composition?

A. No, it doesn't. Par doesn't have a specification for antioxidant firstly because there is no named antioxidant in Par's ANDA product, and secondly because there is no material in Par's ANDA product that's functioning as an antioxidant. So whether named or not named, there was no specification in Par's ANDA product or an antioxidant.

Q. Do you recall Dr. Davies' testimony that the Par ANDA specification allows up to one thousand parts per million for 0.1 weight percent acetaldehyde in the final pharmaceutical composition?

A. Yes, I do.

Q. Do you agree that Par's ANDA products contain 0.1 weight percent acetaldehyde?

A. No, I don't. I think it was set for a specification, but the expectation because of the washing process that we have heard about is that it will be very low or no acetaldehyde in Par's

ANDA product.

Q. And does the not more than one thousand parts per million specification for acetaldehyde include zero parts per million?

A. Yes, it does.

Q. What did you conclude about the function of acetaldehyde in Par's ANDA products from the not more than one thousand parts per million specification?

A. My conclusion it's not there to have a functional purpose, the goal is to keep it to a low level and ideally to reduce it if possible from the formulation, remove it if possible from the formulation.

Q. Do you recall Dr. Davies' testimony that acetaldehyde was present in amounts up to 400 parts per million or 0.04 weight percent in patch samples?

A. I do.

Q. Do you agree that Par's ANDA products contain 0.04 weight percent acetaldehyde?

A. No, I don't. Those are the ones that Dr. DiZio had talked about which were done in his lab with him shaking by hand to his best efforts and

they're not representative of the process in Par's ANDA products so those figures are not relevant to Par's ANDA products.

Q. Are you aware of any batch of Par's ANDA products that has levels of acetaldehyde approaching 400 or 1,000 parts per million?

A. No. The numbers that I presented earlier were the only patches of Par's ANDA products and the highest mean value there was 25 parts per million.

Q. Now, you spoke about the measured amounts of acetaldehyde in batches of Par's ANDA products earlier. Can we put that slide up again. Do these measured amounts of acetaldehyde fall within the claimed range of about 0.01 to about 0.5 percent by weight?

A. No, they don't. So the single largest mean value there as I said is 25 parts per million which is 0.025 percent, which is 25 percent of the lowest range of the claim. And to say that they're numerically about the same would not be right. It's like taking a job that pays a hundred thousand dollars a year and getting paid $25,000 a year and saying you got paid about the

same, it's just not numerically about the same.

Q. Let's go back to your summary of noninfringement opinion. What is your fourth opinion?

A. The fourth opinion is that the amount of acetaldehyde in Par's ANDA products does not meet the about limitation because it does not function to stabilize rivastigmine in the composition.

Q. Did you review any data that informed your opinion as to whether the amount of acetaldehyde in Par's ANDA products function to stabilize rivastigmine?

A. Yes, I have talked about Par's stability data already, but those are the data, yes. So this is the other 25 C data again, I'll talk through it again, but my conclusion was that it's perfectly stable with no acetaldehyde present and acetaldehyde doesn't function to reduce the degradation.

Q. Could you please summarize your reasons why 0.003 weight percent acetaldehyde or less in Par's ANDA products does not meet the claim limitation about 0.01 to about 0.5 weight percent?

A. Yes, I have a slide for that. 0.003 percent is 70 percent less than 0.01, and as I just said, that's numerically not about the same. There is no description in the patent about the use of an antioxidant in 0.003 percent or less. The range limitation was added to enable an amount of antioxidant in the composition to stabilize rivastigmine, so that's why the concentration term was put into the patent.

And applicants did not intend to deviate at the lower end of the range to include amounts that do not stabilize rivastigmine. My understanding is that below the claimed range was not enabled because there was no evidence that it supported the stability of rivastigmine in a pharmaceutical composition.

It would seem to me that the about limitation if it were to be used could only work if it were to stabilize rivastigmine below that range. The Par stability data shows that acetaldehyde at 0.003 percent or less does not function to stabilize rivastigmine in Par's ANDA products so I don't believe it can meet the about limitation if that's related to functionality and

lack of enablement at the bottom end of the range.

Q. Now, in his direct testimony, Dr. Davies discussed a study that he performed. Was Dr. Davies' study relevant to your analysis at all?

A. No, it wasn't.

Q. How would you describe Dr. Davies' study?

A. I would describe it as a nonstandard adaptation of a forced degradation study.

Q. Have you ever seen Dr. Davies' study used before?

A. No, I haven't, I have only seen it here. I haven't seen that kind of study before.

Q. Could you please turn back to tab nine, which is DTX 591 in your binder. Are standard forced degradation studies described in the FDA guidelines?

A. Yes, they are.

Q. Could you please walk us through that?

A. Sure. If you go to page 12 of these guidelines, towards the bottom, it talks about stress testing on drug substance and those are forced degradation studies. And if you could blow

that up. It says these studies are undertaken to elucidate intrinsic stability characteristics, and it says such testing is part of the development strategy and normally carried out under more severe conditions than those used for accelerated tests. So it tells you that these are tests carried out on severe conditions.

The purpose of the test it says below is to provide data on forced degradation, forced decomposition products and decomposition mechanisms for the drug substance.

And it also says that the severe conditions that may be encountered during this process can -- if you carry over to the next page, just to summarized, I should have summarize before I moved on, it says these are severe conditions that are designed to put an extreme stress on to a material and the purpose of that extreme stress is if we go on to page 13, it says, these studies should -- the second paragraph. The first paragraph down.

These studies should establish the inherent stability characteristics of the molecule such as the degradation pathways and

lead to the identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual drug substance and type of drug product.

What it tells you here is the function of the forced degradation study is to use an extreme stress and the extreme stress is to produce a large amount of degradant and the purpose of the large amount of degradant is to allow you to develop your analytical procedures and also to allow identification of the degradants that are being produced.

It further says just towards the end of this section, in a paragraph it says it is recognized, it is recognized that some degradation pathways can be complex and that under forcing conditions decomposition products may be observed which are unlikely to be formed under accelerated or long-term testing. This means that the processes that occur under extreme conditions are understood to give you fast information about degradants, but also understood

to be unreliable and not necessarily predictive of processes and mechanisms that will occur in pharmaceutical products at more conventional conditions.

So this has a particular purpose, the forced degradation studies are understood to have a particular purpose to allow you to identify degradants, but not to allow you to believe that those mechanisms and processes that occur are relevant to what happens in a pharmaceutical product.

Q. Is the standard forced degradation study used in the pharmaceutical industry to identify whether a compound is an antioxidant?

A. No, it isn't. It's used for the function that I just said, and not to investigate adding something into a forced degradation study to see if it's an antioxidant. I haven't seen that done before.

Q. Are there standard parameters for conducting forced degradation studies?

A. No, there aren't. I think we have also heard from other people that your goal here is to produce a large amount of degradant in a very

short period of time and to a very large extent you're left to your own call as to how you might want to do that.

And that would cover the range that Dr. Davies talked about yesterday, very wide ranges of temperature, I think he talked about ambient to a hundred degrees C, I think he talked about a whole range of times from maybe one hour up to a month or something like that, I think it was a very wide range of times he talked about, and obviously a wide range of conditions in the experiment. So you have a pretty much a blank canvas, pretty much an infinite amount of things you can do.

Q. Does the '031 patent provide any guidance for conducting forced degradation studies to determine whether a compound is an antioxidant?

A. No, it doesn't. The '031 patent talks about accelerated testing on the pharmaceutical product with and without an antioxidant which is in my view the correct way of doing this kind of experimentation, it doesn't talk about forced degradation studies which I don't think are how people would do this experimentation.

Q. Is a forced degradation study different from an accelerated stability test?

A. Yes, it is. I tried to explain that, but I will summarize that on a slide that I had, just to be clear. The forced degradation studies are carried out on the active pharmaceutical ingredient. Accelerated stability tests are carried out on the formulations. The conditions for the forced degradation studies are extreme conditions whereas the accelerated stability test, the purpose of those is to speed data collection but to be relevant to the product. Everything you do to speed data correction can make the situation nonpredictable to the product, it's possible. So the more you stress a system, the further you move away from the ambient storage conditions which are the absolute standard you're trying to get to, the less reliable the data will be.

But nonetheless, the goal of the accelerated stability test is to speed data collection but to be relevant to the product. The reason for doing it as I said, the forced degradation study is to make and identify a

degradation product and to allow development. The reason for an accelerated stability test is to assess stability issues and predict realtime performance of product stability and realtime shelf life a slightly accelerated test.

In terms of whether it achieves prediction of a product performance, I think everyone, the FDA guidelines I just read and people working in the field would say that it's unlikely the forced degradation study is going to predict what happens in a pharmaceutical product.

The best expectation you may get is you have the same degradation products obtained from the forced degradation study that you will also see in the product. But in terms of predictions, accelerated stability tests to be predictive of product performance are much more likely as you get closer to conditions of realtime performance and realtime shelf life. In terms of guidance of conditions, the forced degradation study on the API has no fixed method, no clear guidance for the conditions that you would use, whereas accelerated stability test have clear guidance such as the 40 degrees C, 75 percent

relative humidity, but obviously there are options to use other conditions initially to collect data more rapidly, that's possible, but ultimately you would come closer to realtime storage.

And then are these the standard tests to see if something is an antioxidant, forced degradation study is not a standard test for that, whereas an accelerated stability test on a formulation is a standard test for that?

THE COURT: All right. I think we probably ought to take our morning break. We'll take a fifteen-minute recess and then we'll come back.

MR. SILVER: Your Honor, could we have an estimate of the time either before the break or when we resume?

THE COURT: We'll give you one when we come back.

MR. SILVER: Thank you, Your Honor.

(A brief recess was taken.)

THE COURT: All right. Let's be seated.

MS. KOH: Before we continue there

are a couple of exhibits that I have failed to move into evidence, so Par moves DTX 587B which is tab 13 in the binder, and DTX 586B which is tab 14 in the binder.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

MS. KOH: And also I had previously mentioned DTX 617 which is the same as PTX 352 which was admitted into evidence yesterday. And I had mentioned DTX 618 which is the same as PTX 353 which was admitted into evidence yesterday as well.

BY MS. KOH:

Q. Dr. Buckton, do you recall that Dr. Davies discussed the Alsante reference, which is JTX 75, in his direct testimony?

A. Yes, I do.

Q. And did you review the Alsante reference?

A. Yes, I did.

Q. Does the Alsante reference support Dr. Davies' view that his study is a standard test?

A. No, it doesn't. I don't see anything in Alsante reference that describes use of an antioxidant in a forced degradation study, nothing to support that.

Q. Could we please put up slide PDX 115 from Dr. Davies' direct testimony. Do you have a response to what Dr. Davies testified about the Alsante reference on this slide?

A. I think the first sentence, the stress testing is a critical component of drug development is right. That by doing key stress testing you can understand the mechanisms by which an active substance will degrade. And inevitably you do these things for a reason and the reason for the stress testing is it can help you making decisions further downstream.

But I think to highlight stress testing can help in the selection of more stable drug substance salt forms in my experience would relate to a form of degradation which is the degradation in the presence of water. We would change salt forms routinely in the compound relative to hydrolysis. So this relates to a wide range of possible stress tests. It doesn't

relate specifically to oxidative degradation, and once it's clear that a forced degradation study is undertaken to learn about the drug substance and its degradation routes and obviously that learning has to be applied somewhere otherwise it would have been a pointless endeavor. This doesn't give an endorsement of putting an antioxidant into a forced degradation study, that link is not made in this reference really in any of the other references that I have seen.

Q. Dr. Davies also mentioned excipient compatibility test. Can you explain what's an excipient compatibility test?

A. Yes, I can. When you start with first development process, you will maybe have a wide range of excipients which could serve the same function, and it would be sensible to have a way of deciding which was the best one to select for your early formulation development work.

One way we go about doing that is to perform a stress test to see whether the excipient itself causes any degradation of the drug substance. And that would be a crude, rough and ready stress test done by a variety of

different experimental methods and it would allow us to understand whether the drug substance was broken down by excipient A but not by excipient B in which case you would use excipient B in your early formulation work.

The reason for this is to have your first decent go of having a pharmaceutical product. The trouble with the stress test in these condition is you can get false positive results which false positive results are you would see a degradation process occurring in a more extreme stress which wouldn't actually happen in a pharmaceutical product and you could get false negative results and the false negative is the other way, you don't see a degradation process occur in your initial stress test and that ultimately it proves that there was a degradation that happened in the pharmaceutical formulation when you made it.

So excipient compatibility is a rough and ready way by which we limit the first excipients that we will use in our first formulation and we will put that on a standard accelerated stress test and move on from there,

so it's just a crude way.

Q. Are excipient compatibility studies used to assess whether a compound is an antioxidant?

A. I've never seen that done. And the reason for that is you would do your excipient compatibility test with the expectation that you would make a formulation, which was essentially going to be a good formulation in your first effort.

So the goal would be to make something that wasn't degrading. Then when you make your first formulation and you see an issue, if you see some degradation in that formulation, would you then consider resolving that issue? And part of that process for resolving it, if it happened to be oxidation, might include adding an antioxidant.

That's not the only way you would resolve that issue. It's one way you would conceive of doing it.

So the concept of adding an antioxidant would come downstream. It wouldn't be undertaken in an excipient compatibility test because you wouldn't really start off by

formulating to fail.

You would try formulating to get a product that was going to work. If it doesn't work, you would conceive of adding an antioxidant at a later stage.

Q. Is Dr. Davies' study a peer-reviewed study?

A. No, it isn't.

Q. Does Dr. Davies' study allow you to predict what will happen in a pharmaceutical formulation containing a similar amount of acetaldehyde?

A. No, it doesn't. I don't see how you can extrapolate from that test. For a pharmaceutical formulation, you would need to run the test in formulation.

Q. Are antioxidants formulation specific?

A. Yes, they are. So it's possible that one would have an antioxidant that will work in one formulation, but will not work in another formulation. And I have a slide relating to that.

MR. CONDE: Your Honor, we object to to putting up the slide on infringement and part

because we saw this testimony yesterday. This is just a snippet taken out of context. And it just, it is not appropriate for the witness to go up and put up a snippet of a slide out of context in his direct testimony.

THE COURT: All right. Well, I'll overrule the objection.

THE WITNESS: Can I go? Okay.

So this is the deposition of Dr. Frank Theobald, who was the project manager on the Exelon project. And he was asked, To reduce the degradation of Rivastigmine, you'd have to select an antioxidant that was effective with respect to Rivastigmine; right?

And his reply was: That's not correct. What I'm saying, it must be effective for the API in combination of the formulation the API is composed in, which is in line with my view as well that antioxidants are formulation specific. And whether they will work in a formulation is something that you need to investigate.

Q. Do you have an example of a formulation where one antioxidant works, but another

antioxidant doesn't?

A. Yes, I do. And I think we've seen it earlier, but it's -- and I've answered it.

Q. And can you please turn to Tab 15 in your binder?

MR. CONDE: Your Honor, we object to the use of this exhibit. It was not cited in his expert report for any purpose.

THE COURT: Is that right?

MS. KOH: Dr. Buckton's expert report on Paragraph 87 cites the testimony of Dr. Ogorka and the testimony cited in that paragraph is referring to this document, which is DTX 80, which was Ogorka Deposition Exhibit 1.

MR. CONDE: The problem with that, Your Honor, is we don't know how Dr. Buckton is going to use the exhibit.

THE COURT: All right. Well, I'll overrule the objection. Go ahead.

BY MS. KOH:

Q. What is this document, DTX 80?

A. This is a fax from Dr. Ogorka with a Market Formulation Development Report from LTS.

Q. And if you could please turn to Page

55051.

A. What was the number? Sorry.

Q. Sure. 55051.

Could you please describe this study?

A. Yes. This was a study of a formulation, which was called 2200. And that formulation was found to degrade to two oxidative degradation products that we've already heard and spoken about, the ketone and the styrene. 2.8 percent of ketone and 2.26 percent of the styrene.

Similar formulation was made with 0.1 percent tocopherol included and the degradation reduced to 0.29 percent for the ketone and 0.66 percent for the styrene.

Similar formulation was made this time including 0.1 percent ascorbyl palmitate, which is another one of the antioxidants listed in the '031 patent. And this time the ketone went to 0.78 percent. So it was lower than the 2.8 where no antioxidant was present.

The styrene went to 2.82 percent, which is slightly higher than the 2.26 percent with no antioxidant was present. And then the

final formulation was a combination of the two antioxidants 0.1 percent of ascorbyl palmitate and 0.1 percent of tocopherol. This time the ketone was 0.61 percent rather than 2.8 percent and the styrene was essentially unchanged at 2.18 percent rather than 2.26 percent.

And what these data show to me is that the alpha tocopherol was effective in reducing the oxidative degradation formulation, the formulation that was included by itself and the low level of degradation, substantially low.

The ascorbyl palmitate was not effective in reducing the oxidative degradation because one of the degradants remained higher, maybe slightly higher, but essentially remains very high. And to have one degradation very high degradant is as bad as you need.

It's not successful if you have one degradant which is reduced a bit and one that stays high. You really need to reduce the degradation of both degradants. And ascorbyl palmitate and alpha tocopherol together didn't perform as well as the alpha tocopherol alone, and they were somewhere in between the ketone and

pretty much no improvement for the styrene degradant.

So what we can see here is the alpha tocopherol worked. Ascorbyl palmitate didn't work. And the combination of the ascorbyl palmitate and alpha tocopherol didn't work.

And so what it shows to me is what I've been talking about just now is that an antioxidant in a formulation has to be investigated to see if it works. And it isn't necessarily true that any antioxidant will function in any formulation.

MS. KOH: Par moves the admission of DTX 80 into evidence.

MR. CONDE: Subject to our objection, Your Honor.

THE COURT: All right. Admitted over objection.

BY MS. KOH:

Q. Did plaintiffs also conclude whether ascorbyl palmitate was unsuitable as an antioxidant?

A. Yes, they did. And the deposition testimony we just talked about made that

conclusion.

This was Dr. Ogorka's deposition testimony, and talking about these data. The underlined bit I have, he talked about the unsuitability of ascorbyl palmitate.

And the follow-up question was: Is ascorbyl palmitate a suitable antioxidant for Rivastigmine? And his answer was, ascorbyl palmitate looks like not to be suitable for the purpose.

So his conclusion was the same as mine.

Q. Do you have an example of an active pharmaceutical ingredient that required an antioxidant in one formulation to be stable, but did not need an antioxidant in another formulation?

A. Well, the example would be the Exelon patch and Par's ANDA product. The Exelon patch does require an antioxidant and Par's ANDA product does not require an antioxidant.

Q. What is your final conclusion as to whether Par's ANDA products infringe Claim 7 of the '031 patent?

A. My conclusion is they do not infringe.

Q. Could you please turn to Tab 16, which is JTX 2 in your binder? And what is this document?

A. This is the '023 patent.

MS. KOH: Par moves admission of JTX 2 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: All right. Why are we doing this, Ms. Koh?

MS. KOH: It's for our declaratory judgment of noninfringement on the 4.5.

THE COURT: I don't remember, but I thought we decided that we'd know the answer to -- whatever the answer to that case is whatever happens in response to this case.

Am I wrong?

MS. KOH: We just have one question on that.

THE COURT: All right. Let me just ask: Am I remembering this wrongly?

MR. CONDE: No, Your Honor, I believe you recall correctly.

THE COURT: All right. Well, I

guess you're ready to ask a question. You might as well ask the question.

But I reserve the right to strike it after you do so. Okay?

MS. KOH: Okay. Your Honor.

BY MS. KOH:

Q. Dr. Buckton, do you have an opinion as to whether Par's ANDA products infringe the claim of the '023 patent?

THE COURT: Okay. Well, actually I'm going to strike the question because that makes no -- it makes no sense to be asking that, unless you're going to try that here. And you're not trying that here.

MS. KOH: Okay.

THE COURT: Okay?

MS. KOH: Okay.

THE COURT: I mean, we did say this at the pretrial conference.

MS. KOH: Okay. I just wanted to make sure in case we needed something in evidence.

THE COURT: Okay. Just to state to make sure that I'm not misremembering things, Mr.

Kallas or somebody, if I decide or it is decided by whoever makes a decision that the Par products don't infringe Claim 7 of the '031 patent, there's a stipulation that they don't also infringe any claims of the '023 patent?

MR. KALLAS: With the exception of the 13.3 product isn't in this case.

THE COURT: Which said if it became relevant we'd have to expedite a trial on that?

MR. KALLAS: I think that's correct, Your Honor.

THE COURT: Okay.

MR. KALLAS: That's my recollection.

THE COURT: Well, in any event, you're the representative of Novartis, so you're --

MR. KALLAS: Yes, Your Honor.

THE COURT: Okay. Thank you.

Go ahead, Ms. Koh. Onto something else.

MS. KOH: Okay. No further questions with respect to infringement.

THE COURT: All right. Thank you, Ms. Koh.

Cross-examination.

MR. CONDE: May I approach, Your Honor?

THE COURT: You may.

MR. CONDE: I have a stack of binders, unfortunately.

CROSS-EXAMINATION

BY MR. CONDE:

Q. Good morning, Dr. Buckton.

A. Good morning.

Q. Nice to see you again.

A. And you.

Q. Let's discuss your background first. You're not a chemist; correct?

A. I'm pharmaceutical formulator, so I do physical chemistry. I don't do synthetic chemistry.

Q. And you don't talk about structures of compound because generally that's not your thing; right?

A. That's quite right.

Q. And apart from this case you would not generally know the structures of impurities of rivastigmine; right?

A. That's right.

Q. And you're not qualified to opine on a mechanism of oxidative degradation; right?

A. That's quite right.

Q. You have not done any work on oxidative degradation on active ingredients in transdermal devices; right?

A. So I didn't quite catch your question.

Q. Sure. You have not done any work on the oxidative degradation of active ingredients in transdermal devices?

A. I don't remember whether I have. I don't think I have. We have worked on transdermal devices within Pharmaterials, but I don't know that we have done oxidative degradation of that, so I think that may well be true.

Q. You know there is a list of antioxidants in the '031 patent?

A. I do, yes.

Q. And you know those antioxidants all work in different ways?

A. I do know they work in different ways, yes.

Q. And you're not able to tell me how each of those antioxidants are meant to act?

A. I am -- as I think I have talked about before, I don't keep kind of an encyclopedia record of how each antioxidant functions in terms of its mechanism. I know a few of them. If you put a whole list in front of me, I couldn't do them all. If you put a list of maybe ten, I won't get them all.

Q. You don't get bogged down with how different antioxidants are meant to function; right?

A. That sounds good to me. I think that's right, yes.

Q. Now, Mr. Hoy, could you please go to slide PDX 201. And you're familiar with Claim 7, right, Dr. Buckton?

A. Yes, I am.

Q. And I think you said it's your view that if a compound is an antioxidant in a formulation, first the formulation without an -- let me start over.

I think it's your view that in determining whether an antioxidant is needed,

first you must know that the formulation without an antioxidant must show significant degradation; right?

A. To know whether an antioxidant is needed, for me, you add an antioxidant if you have significant degradation, if you don't have significant degradation, you don't add an antioxidant, so that sounds correct.

Q. So Claim 7 doesn't have a requirement that there be a significant degradation without an antioxidant; right?

A. Claim 7 just talks about the range in which an antioxidant would be present. It doesn't talk about a significant degradation, no. I guess I should say that I just said in my direct that I believe the about limitations on that certainly below must relate to functionality.

Q. But my question was directed to whether there needs to be significant degradation without an antioxidant to meet the requirements of Claim 7. There does not, correct?

A. I think there might in relation to about.

Q. Put aside about, other than that, there is

not; right?

A. Well, so you want me to do part of Claim 7?

Q. Well, I want you to consider the .01 to .5.

A. Without the about?

Q. Right.

A. I think I'm less clear on whether -- I'm sorry, I have forgotten your first question.

Q. Does Claim 7 require significant degradation with the absence of an antioxidant?

A. The meaning of antioxidant is not linked to a function, but in terms of the concentrations, I'm not so clear. What I read from the file history, it does seem to me to be a functional concentration.

Q. Claim 7 doesn't use the word significant degradation anywhere in it, does it?

A. I can agree that Claim 7 doesn't use the word significant degradation.

Q. And Claim 7 doesn't say anything about comparing formulation with an antioxidant and without an antioxidant; right?

A. The claim itself doesn't, in terms of

understanding how you may or may not fall within the claim, perhaps you do.

Q. And there is no stability requirement in Claim 7, either; right?

A. Outside of what I have just talked about in my direct, talked about the meaning of about and the concentration range which I think does have a stability requirement.

Q. Aside from that, there is no stability requirement in Claim 7; right?

A. It's a little difficult to do aside from that, because that's part of Claim 7, but if we strike that bit that's highlighted out, without that bit that's highlighted that's true.

Q. Claim 7 doesn't make mention the word stability; right?

A. Well, I think I have explained in my direct and I think about 0.01 to about 0.5 percent by weight because of my link to look at the file history would suggest that does relate to functionality and stability.

Q. When the court construed Claim 7, no where in that construction does it use the word stability?

A. The construction was for antioxidant as I understood it.

Q. And it doesn't include the word stability?

A. The word antioxidant did not include the word stability.

Q. And the word antioxidant did not include the term shelf life?

A. Construction of the word antioxidant did not include the word shelf life.

Q. Now, you agree that reducing agents are one type of antioxidant; right?

A. I have agreed that some antioxidants are kind of like if you like sacrificial antioxidants, they could be called reducing agents, as opposed to all reducing agents are antioxidants.

Q. And ascorbic acid is a type of antioxidant that is a reducing agent; right?

A. That's true.

Q. Now, Mr. Hoy, could you go to slide PDX 204. And PDX 204 is from page 003 of Modern Pharmaceutics, which is JTX 106. You can use the book, but we can just look at the screen would probably be easier.

And the heading on that page reference to antioxidants; right. You may have to look at the actual document, I apologize.

A. Where is the actual document?

Q. JTX 106 in your book.

A. What page number is that, sir?

Q. Page 203.

A. Thank you.

Q. I think we have put the actual document the screen.

The heading on page 203 says antioxidant and chelating agents; right?

A. Yes.

Q. And the first sentence says antioxidants and chelating agents are used to protect drugs against autoxidation; right?

A. Right.

Q. I think you made reference to that, the sacrificial oxidation concept; right?

A. Correct.

Q. And it goes on to say --

A. That's one way antioxidants work, see, sorry to interrupt.

Q. It goes on to say, "Mechanistically, some

antioxidants, such as ascorbic acid, ascorbyl palmitate, sodium bisulfite, sodium metabisulfite, sodium sulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thioglycerol, and thioglycolic acid, act as reducing agents." Right?

A. Right.

Q. And this also says that some antioxidants -- so this says that some antioxidants may be reducing agents; right?

A. That's correct.

Q. And in the next sentence on page 203, a reference which you rely on, says these antioxidants quote are easily oxidized, preferentially undergo autoxidation, thereby consuming oxygen and protecting the drug or excipient. Do you see that?

A. I do.

Q. So again, that means that the antioxidant undergoes oxidation before the compound to be protected is oxidized; right?

A. For those ones listed there.

Q. Let's go to page 183 in the document itself, please.

A. Yes.

Q. And could you blow up -- yes, table two.

So table two lists some functional groups that undergo autoxidation; right?

A. That's the heading, yes, indeed.

Q. That means these compounds are reducing agents that could undergo oxidation before the compound to be protected is oxidized; right?

A. Well, I think these are functional groups of compounds, some of those compounds containing these functional groups could be in that class.

Q. And one of the functional groups is aldehyde; right?

A. Yes.

Q. They give a specific example of paraldehyde?

A. Yes.

Q. And acetaldehyde is an aldehyde; right.

A. Yes.

Q. You agree that Modern Therapeutics is a standard reference that people in your area would use?

A. I think it's Modern Pharmaceutics, it is a standard reference.

Q. Now, Mr. Hoy, could you please go to DDX 227. And on direct, you said acetaldehyde has never been used as, and is not recognized as an antioxidant; right?

A. Yes, I was talking through my understanding of my pharmaceutical experience, correct.

Q. Could you please turn to what's been marked as PTX 401 in your exhibit book?

A. PTX 401?

Q. Yes. Which has been marked for identification as PTX 401. And this is --

MS. KOH: We have an objection to the use of PTX 401, the document that was discussed earlier was excluded by Your Honor early this week, or last week, and we believe it also should be Plaintiffs: Excluded under Rule 37(b)(1).
Defendant: Excluded under Rule 37(c)1 as not timely produced to Par.

THE COURT: Well, I'm going let Novartis ask some questions about this, and right now we're on cross-examination, and we'll see, but feel free depending on what they do to renew

your objection.

BY MR. CONDE:

Q. Dr. Buckton, you see there is a Chinese patent and if you turn about halfway through it, you'll see an English translation. Could you go to the English translation, please. Are you there, sir?

A. I am, yes.

Q. And you see that this is patent number ZL 92108440.4. Do you see that?

A. I see that, yes.

Q. And publication date is October 7, 1998?

MS. KOH: Your Honor, we also object to the use of the translation of the Chinese document.

THE COURT: All right.

MS. KOH: It's not a certified translation, Your Honor.

THE COURT: Well, for purposes of cross-examination, I'm going to let him continue, but again, feel free to renew your objection in a little while. Okay.

Q. So, Dr. Buckton, the publication date is October 7th, 1998; right?

A. That's what it says.

Q. And have you seen this document before?

A. No, I haven't.

Q. Did you run any searches as part of your work to find out if acetaldehyde had ever been referred to as an antioxidant?

A. I did a search of the FDA inactive ingredient list and found nothing there. I searched the Handbook of Pharmaceutical Excipients. And, otherwise, I am not sure if I did a search of the pharmaceutical literature.

I was using my experience, 30 years as a scientific formulator.

Q. So you only looked at the FDA excipient list and, excuse me -- yes. The FDA list and you also looked at -- let me restate that.

So you only looked at the FDA inactive ingredient list and the Handbook of Pharmaceutical Excipients list; right?

A. I can't swear that's true. I don't know if I did another search. It was a long while ago.

Q. So, as far as you recall today, you don't

recall looking at -- doing any other search?

A. I don't recall, one way or the other, I'm afraid. It was a long while ago, but I certainly came to view that it hadn't been used.

And all my years of experience was such that, you know, my work as a formulator that I hadn't seen it used.

Q. So could you turn to Page 6 of the English translation, please? And could we blow up the last paragraph on Page 6?

And the last paragraph on Page 6 of this Chinese patent says "said antioxidant and anti-mildew stabilizer is an aldehyde solution such as formaldehyde, acetaldehyde or a combination thereof, it functions to prevent decomposition of iodide and mildewing of chromogenic agent, caused by the presence of air or oxygen dissolved in the system.

Do you see that, Dr. Buckton?

A. I see those words. Yeah.

Q. Prior to today, you hadn't read this paragraph; right?

A. Prior to today, I -- in fact, any time. I'm not sure I would read a paragraph in a

Chinese patent on the particular Quick Testing for water purification and preparation method thereof.

I don't know why anyone in my field would look at a patent that says that.

Q. Par's lawyers didn't show you this document in the last several days?

A. I haven't seen this document.

Q. Did they talk to you about the document?

A. I have heard there was a document.

MS. KOH: Objection. Sorry. I object to counsel's request to ask for privileged conversations between counsel and --

THE COURT: I don't think -- under the circumstances, I'm going to overrule that objection.

Go ahead.

BY MR. CONDE:

Q. Okay. So Dr. Buckton, did Par's ANDA lawyers talk to you about this document?

A. Not about this document. I've heard there was a document that there was debate about whether it would be introduced or not, but I haven't seen this document or talked about this

document.

Q. And you heard that the document mentioned that acetaldehyde is used as an antioxidant -- can be used as an antioxidant; right?

A. Well, I haven't heard about this document, so it wasn't put before me. My understanding was it was a discussion that happened and it wasn't going to be included.

Q. Okay. So, Dr. Buckton, let's look at the stress testing discussed in the '031 patent. Can we go to JTX 1, Column 4, Lines 20 to 25, please, up on the screen?

And in this section, it says that without an antioxidant, degradation products were 4.46 percent; right?

A. That's correct.

Q. And it says that the degradation products with an antioxidant were 1.3 percent; right?

A. That's correct.

Q. And when you read this, you understand that when they're referring to degradation products, they were referring to at least Impurity 4 and ECAV?

A. I don't know that I've looked into that,

but I don't see why that wouldn't be the case.

Q. And they were comparing the total amount of degradation products with and without an antioxidant; right?

A. Well, the outcome having degradation products. I have no more information from that paragraph to help me with that. That's total for sure, not individual named ones.

Q. Now, you agree that the purpose of Par's stability testing was to assess the long-term stability testing of this product; right?

A. That's right. Yes.

Q. And when you measured the long-term stability testing, it relates to shelf life; right?

A. Ultimately, it does. Yes. That's the goal of that kind of experiment. Correct.

Q. And shelf life refers to the time period over which products remain suitable for commercial use; right?

A. Ultimately, that's true. Yes.

Q. And there's no analogy between the test in the '031 patent and the stability testing that Par did on its product; right?

A. There's no analogy between? Sorry.

Q. There's no analogy between the test in the '031 patent, the stress testing in the '031 patent and the stability testing on Par's products; right?

A. Well, there's an analogy in as much as what they've done here is undertake the stress condition where they've undertaken a condition that's a 40, 75. So, in respect to them moving to the conditions that were used in Par's ANDA product, there is an analogy.

But in terms of the numbers here for the degradation by products, there's nothing because this data here is 40 degrees C, for example.

Q. And stress tests like those in the '031 patent are entirely unrelated to the concept of shelf life, which was the purpose of Par's stability testing; right?

A. I think it's unfair to say they're entirely unrelated to the concept of shelf life. I think the purpose of this kind of study in the patent is to point us in the right direction.

Clearly, for the patent application,

they're not going to wait two years and run a full shelf life.

Q. All right. So, Dr. Buckton, could you please turn to what I think is Tab 3 of your deposition book, which is the deposition that was taken on April 4th, 2014? And turn to Page 106.

A. Please.

Q. Can we have that up on the screen? It may be easier to follow it on the screen, if you'd like.

So starting at Line 8, you were asked to turn to paragraph --

THE COURT: Mr. Conde, hold on a second.

THE WITNESS: The screen is a little blurred so I want to find it on the text.

BY MR. CONDE:

Q. Page 106 about Line 8.

A. All right.

Q. You can see at Line 8 this is -- just to set the context of the question, after that --

A. Okay.

Q. -- and in Line 8, it says, You cite two examples from the '031 patent in Paragraph 34?

And you answered, Yes.

Do you see that?

A. Yes, I do.

Q. And you can see from the context here that the two examples are the same two examples we were just talking about from Column 4, Line 20 to 30 regarding the stress testing; right?

A. Well, I see the numbers therein and the next question. So, yes, that possibly is true. Yes.

Q. So let's continue on to Page 107, Line 15. Are you with me, Dr. Buckton?

A. 107, 15?

Q. Yes.

A. Yes.

Q. And starting at Line 15 on Page 107, you were asked, "But when there is one percent, 1.09 percent degradation, tocopherol was able to reduce that degradation to 0.25 percent degradation; correct?

"Answer: Sure. But that's totally unrelated to the concept of an -- of a shelf life of a product. This is a very short exposure to a certain set of conditions and that's entirely

unrelated to the concept of shelf life.

So that one percent has no meaning in -- in any analogy to what's happening in Par's product. Okay.

This is an indication that, in this particular test, the degradation was reduced, that that is what they're talking about here. There's no analogy at all to Par's product.

"Question: So when there was -- excuse me. So whether there was degradants -- degradation, tocopherol was able to reduce the degradation in the example of the '031 patent?

"Answer: That's correct. But shelf life is un -- is an unrelated concept."

Were you asked those questions and did you give those answers?

A. I think that's -- that is true, but it's out of context, I think, in relation to what I was talking about.

Q. Okay. Your counsel can do it on redirect. I'm on a clock here. If he wants to redirect, he can.

Okay. So let's now turn to Slide DDX 242. And on your direct testimony, you made

reference to this question and answer from Dr. Theobald; right?

A. That's correct.

Q. And you didn't put up his entire testimony, did you?

A. I just put this slide up. Yes.

Q. And you know that there's more testimony that he gave that was played in Court yesterday?

A. I heard that, yes.

Q. Well, you were here for it; right?

A. Yes.

Q. And this testimony relates to whether an antioxidant is effective; right?

A. That's correct. Yes.

Q. Whether the formulation was stable in a commercial sense; right?

A. I don't know ex -- I don't know that it's necessarily in a commercial sense, but it's effective in the formulation is what he was talking about.

Q. So you can't tell whether he's talking about in a commercial sense or whether he's talking about in some other sense; right?

A. At the moment, I can't. It may be.

If I look further, I might be able to, but just now I can't.

Q. So let's go to DDX 244. You also put this quote from Dr. Ogorka; correct?

A. Correct.

Q. And, again, you didn't provide all the testimony that he gave in his deposition that was played in Court yesterday, did you?

A. No. This is an excerpt.

Q. And when he was talking about the unsuitability of ascorbyl palmitate, he was talking about from a commercial perspective; right?

A. I don't remember him saying that. But if he did, I can be corrected. But I don't remember him saying so.

Q. So you can't tell from this quote whether he's talking about in a commercial sense or some other sense, can you?

A. I don't remember him qualifying it. I'm just taking the quote as it stands.

Q. Right. But from this quote, you can't tell whether it's a commercial sense or some other sense, can you?

A. Well, there's no qualifications, so I can't tell you anymore than the quote. I'm just telling you what he said, and what he said is in keeping with my thought on the subject.

Q. Okay. And you can't tell whether -- you know, whether he was talking about the use of ascorbyl palmitate at 0.1 or some other concentration; right?

A. I believe he was talking about data that I've been talking about so that would have --

Q. So it's possible to increase the amount of ascorbyl palmitate and still be within the claims of the '031 patent; right?

A. Well, I guess it's possible to do more experimentation to -- to explore other options. But based on the data that were available, I think this was his conclusion.

Q. So now, let's talk about Dr. Davies' -- one second.

So let's talk about Dr. Davies' scientific testing. You respect Dr. Davies as a scientist; right?

A. I do.

Q. He's thought of highly by the scientific

community; right?

A. I do. I do. That's not the right answer. I think he is. Yes.

Q. We're not getting married today.

A. No, that's fine.

Q. And you know that Dr. Davies conducted specific tests to determine whether acetaldehyde is an antioxidant; right?

A. I know he carried out tests and I've explained why I don't believe they're relevant. Yes.

Q. And you did not do any testing or experiments in response to Dr. Davies' testing, did you?

A. No. I looked at the Par's ANDA data.

Q. But you didn't personally do any testing to respond to Dr. Davies' testing; right?

A. So I didn't feel the need to, after having looked at Par's ANDA data.

Q. And you didn't do any testing yourself on Par's product in response to Dr. Davies' testing; right?

A. I didn't feel the need to after looking at the ANDA data.

Q. Now, you said that Dr. Davies' test is a non-standard test; right?

A. That's correct. Yes.

Q. And on direct, you went to the FDA guidelines for support of that; right?

A. I went to the FDA guidelines to provide a description of what the forced degradation study is.

Q. And you say that Dr. Davies' testing is not reliable based on the FDA guidelines of forced degradation testing; right?

A. There is another step between the two, I went to the guidelines to say what a forced degradation study is. I said I never seen anyone add an antioxidant to the forced degradation study, and given that forced degradation study itself is inherently unreliable, I also believe that adding an antioxidant to a forced degradation would be unreliable, too.

Q. And the only basis that you say that the forced degradation is unreliable is the FDA guidelines; right?

A. The FDA guidelines I was using to demonstrate the fact that it isn't just my

opinion that that would be the case, it's an general view.

Q. Dr. Buckton, that's not my question. In your expert report, the only reference that you rely on for your opinion that forced degradation stress studies are unreliable are the FDA guidelines; right?

A. In my report that may well be true.

Q. Let's go to those guidelines. It's at DTX 591, please, and go to page 13. We can put it up on the screen.

A. Is it in my direct folder?

Q. It's in your direct at tab nine?

A. Tremendous. Thank you.

Q. We can put it up on the screen, DTX 591.

A. What page was it?

Q. Page 13.

A. 13.

Q. Okay. So we're going to do this the old fashion way -- oh, it's coming up? There we go. Great. Let's go to page 13, please. And it looks like we have another -- there is a paragraph that says it is recognized in the middle. Right there. Can we blow that up more

or not? Excellent.

So if you look at the very first sentence in the paragraph, it says it is recognized that some degradation pathways can be complex and that under forcing conditions decomposition products may be observed which are unlikely to be formed under accelerated or long-term testing. Do you see that?

A. Yes, I do.

Q. And that's the only sentence from this guidelines that you quoted in your expert report for support that Dr. Davies' stress testing is unreliable; right?

A. That's the only thing I quoted for saying that forced degradation studies are how I described.

Q. And let's look at the sentence a little more closely. It says under forced conditions, decomposition products may be observed which are unlikely to be formed under accelerated or long-term testing; right? Do you see that?

A. Yes.

Q. Dr. Davies when you did his stress test, the two impurities that he looked at were

Impurity 4 and ECAV; right?

A. Those are the two he looked at. I was here when Dr. Ganem talked yesterday and I'm not going to talk about his mechanism, but my understanding was he said there was a large number of other degradants produced, too, but that's not what I'm going to testify to.

Q. I don't think he actually said how many degradants there were in addition to those, but you agree that Dr. Davies' testing resulted predominantly in two impurities, Impurity 4 and ECAV?

A. I think from my listening to Dr. Ganem that sounded correct. I think he said there were large amounts of those and large amount of other ones, too, but we would have to go to his testimony, not mine in relation to those degradants.

Q. You agree that Impurity 4 and ECAV were identified in Par's stability testing in both accelerated and long-term testing; right?

A. I agree that they were identified. I think the spirit of this document is clear in that the mechanism can change by doing the

extreme conditions and that can give rise not only to the ones that you wanted to see, but to other degradants arriving to suggesting that you change the mechanism. That's the way the document reads and that's my understanding of it.

Q. But regardless of with respect to Dr. Davies' testing, he obtained the same two impurities that were found in Par's stability testing, namely Impurity 4 and ECAV?

A. As I said, I think he found other things, too, so it doesn't mean to me it isn't -- I'm not a chemist to do such discussions, but it doesn't mean to me the mechanism of getting there was the same.

Q. So you're not able to provide an opinion whether Dr. Davies' stress testing is reliable because you don't understand the mechanism of the stress testing that he undertook; right?

A. No, I don't agree with that. I think I can give a very clear answer why I regard it as unreliable and I think Dr. Ganem can talk to you about the mechanism. For me the mechanism doesn't matter, what matters is can you rely on these kind of tests generally for a

pharmaceutical product and my understanding is you can't.

Q. And your understanding is only based on this one sentence; right?

A. This is a distillation of this knowledge.

Q. Let's move on to Par's stability testing. The stability testing was done from nine batches of Par's product; right?

A. I think that's correct.

Q. And in those nine batches, they had between 30,000 to over 270,000 patches per batch, do you recall that?

A. They had thousands. I don't know how many.

Q. You'll take my representation that you went through this in your deposition you recall?

A. I didn't know the number then either, I still don't. I have got no reason to doubt your number. If it's wrong, I'm sure someone will point it out.

Q. Mr. Hoy, could you go to slide PDX 205.

And Dr. Buckton, you recognize this as part of the specification protocol for Par's ANDA product; right?

A. I do.

Q. And this page tells us how Par studies the impurities when conducting its stability testing; right?

A. Well, it has some aspects of that, yes.

Q. Fair enough. And what it tells us is that when it looks at Impurity 4 and ECAV, it only tested one patch per batch at any particular time; right?

A. That's correct, the testing protocol is one patch will be pulled at each time point throughout a stability study, that's my understanding of it.

Q. When you did your analysis in this case, did you not conduct any statistical analysis of the data from Par's stability testing with respect to Impurity 4 or ECAV; right?

A. We did talk about this in the deposition, too, obviously, but the two batches for which there was no detectable or zero acetaldehyde, had no degradation, either, at ambient storage conditions, and I don't understand what kind of test I can do to show that something reduces the degradation when there is no degradation. It's

impossible for me to conceive a statistical test to show that you can do that.

Q. So let's move on and talk about the stability data that you examined.

And let's go to PDX 206. And PDX 206 is information from your expert report; correct?

A. I don't know. It may be. I can have a look if you want, but I can trust you for it, I'm sure.

Q. I'm sure your counsel will tell me if I'm wrong.

A. I'm sure.

Q. There is table one, and table one is stability data for lots containing no acetaldehyde stored at 40 degrees C, 75 percent relative humidity. Do you see that?

A. I do. I was trying to find the reports. Which report was it from? Sorry.

Q. This is from your rebuttal report.

A. Okay.

Q. And it shows in table two stability data for lots with detectable acetaldehyde stored at 40 degrees Celsius, 75 percent relative humidity,

do you see that?

A. Just looking through my records, these are a couple of data points selected from the table in my report.

Q. Correct.

And the first chart is for lot 110111, and it provides data from the stability test for Impurity 4, ECAV, and rivastigmine, initially and at twenty-six weeks. Do you see that?

A. Just so I'm clear, on my report at C in table one in paragraph 38; is that correct?

Q. Yes.

And that data is correct; correct? We have put the correct data for week 26 that's up in yellow there?

A. Yes, that's correct.

Q. Okay. And then table two is data from lot 130108, and again --

A. Sorry, one second, I'm not sure it is correct, actually. I might be wrong. I'm struggling. It is C, is it?

Q. Right.

A. Is it not true -- I'm sorry, I'm looking

at the wrong bit. I'm just trying to translate from my table to your table. I do agree now it is correct.

Q. Thank you very much.

And then we also have table 2C and we have lot 130108, and again we have the information from your chart for Impurity 4, ECAV and rivastigmine, the initial measurements and the twenty-six weeks measurements; right?

A. That is rather better this time. I'm with you already.

Q. Thanks.

If we look at the data of impurity of week twenty-six for 110111, the total degradation at week twenty-six is .3; right?

A. If you take that point of isolation, that is correct.

Q. If you look at the data with acetaldehyde at week twenty-six, the amount of total degradation is basically less than .1; right?

A. Yes. Again, that's taken one point in isolation, which I think I said at the deposition I wouldn't do.

Q. So if you compare those two batches, it

shows there is a reduction in the amount of oxidative degradation in batch 130108 with acetaldehyde versus batch 110111 without acetaldehyde; right?

A. No, I don't conclude that now or at my deposition, because if you take the data set as a whole, which is the right thing to do, so the table, it says -- never mind, if you take the data as a whole, for 40/75 and my report actually says 45/70, it said 40/75, take the data as a whole for 40/75 accelerated stability test, these are both stable and inevitably some degradation will kick in toward the end of this.

I don't accept you can interpret a meaningfully thing from one point of an end of a data set such as this. If you run them longer, both of them will degrade. It's a point in time and not a review of the whole data set.

Q. Stick with this data that we have that we're looking at with acetaldehyde versus without, and from this data, you can't conclude whether acetaldehyde reduces oxidative degradation or does not reduce oxidative degradation, just from this data; right?

A. Well, I wouldn't. So I would look at the whole data set.

Q. And you didn't actually do any statistical analysis on the whole data set, did you, Doctor?

A. I think I explained that. If you take the kind of gold standard test, the ambient conditions, and you have zero degradants throughout the entire shelf life period, how can you demonstrate something has reduced the degradation when it was zero? I don't understand how you can do that.

Q. You can't use the data set to show that acetaldehyde reduces the degradation of impurities; right?

A. You can't -- you can show that it doesn't reduce it, you can't show that acetaldehyde -- what did you say?

Q. You can't show either way whether it reduces or doesn't reduce that because the way the data is; right?

A. If in ambient conditions, the data are perfectly stable, you can't improve on that, so acetaldehyde cannot reduce the oxidative degradation.

Q. That wasn't my question. I'm talking about stability data. I'm trying to find out whether you can do a statistical analysis based on any of the data set proving with certainty, statistical significance as Dr. Michniak-Kohn said that, in fact, acetaldehyde does not act to reduce oxidative degradation?

A. I think as I just said, I don't see how I can do that given the best data I can possibly use, the room temperature data and for all of the data points for both of the samples with no detectable acetaldehyde I have no degradation, how can I do any test on that? The data are so stable, I can't do anything with it. It's just so clear.

MR. CONDE: I have no further questions at the time, Your Honor.

THE COURT: Thank you.

Any redirect?

REDIRECT EXAMINATION

BY MS. KOH:

Q. Dr. Buckton, you recall when counsel pointed you to your deposition starting at page 106?

A. Yes.

MR. CONDE: Your Honor, I don't believe she is allowed to rehabilitate Dr. Buckton based upon going back to his deposition transcript. You can ask whatever question you want to clarify, but I don't believe it's proper to use deposition transcript on redirect.

THE COURT: Overrule.

BY MS. KOH:

Q. You wanted to explain the context of your answer. Would you like to explain the context of your answer?

A. Am I allowed to look at this or not?

THE COURT: Yes, you can look at it.

A. Okay. So I believe, I won't go back and read it in any detail, but I do believe that our discussion was about the amount of degradation that had been produced, and the amount of degradation that was allowable in Par's ANDA product, which is a very different product to the product that's being discussed in the patent application.

And in my view, I was being asked to

link the data in the patent application for a completely different product in terms of numerical values there to the data in Par's ANDA product when the numerical values have a very clear meaning in terms of shelf life.

So if there was any confusion between us, then that's unfortunate, but my understanding was we were trying to link those two things together and I was trying to demonstrate that the numbers in one particular formulation in the patent are not related to any aspect in relation to Par's specification for shelf life. That was the -- where I was in my discussion and my thinking and I don't think that's how it was represented to me when we just had a discussion a few moments ago.

MS. KOH: No further questions on redirect.

THE COURT: Thank you, Ms. Koh. Thank you, Doctor. You may step down. Thank you.

MS. KOH: Dr. Buckton is our next witness.

THE COURT: You may step back up.

So you're still sworn.

Go ahead, Ms. Koh.

DIRECT EXAMINATION

BY MS. KOH:

Q. Dr. Buckton, if Dr. Davies is correct that acetaldehyde is an antioxidant, do you have any opinions as to whether the '031 patent is valid or not?

A. Yes, I do. And I have a slide that because of the written description, definite and enablement requirements, if acetaldehyde is deemed to be within the claims I would regard it as invalid.

Q. Now, let's discuss written description first. Did you consider the standard for written description in your analysis?

A. The standard I considered is on the slide, and I was considering patent specification must allow one skilled in the art to recognize that the patentees invented what is claimed as of the time the patent application was filed.

Q. Would a person of ordinary skill in the art understand that acetaldehyde was described in the '031 patent as an antioxidant?

A. No, they wouldn't. Firstly, for the reasons that I did talk about earlier in relation to why I don't view acetaldehyde as an antioxidant. But also because the patent lists materials that are an antioxidant.

Q. And could you turn to that -- discuss that list of antioxidants?

A. Yes, indeed, so it's column four, lines 10 to 15 and I already talked to this, so I won't read the whole list of antioxidants again, but the language is that the antioxidant is selected from, and then it describes the list, and for me reading the patent, this language is very different to the other language I see in the patent, so if I look where other materials are described in the patent, I have other slides for these, as they come through

A. Everywhere else -- this is at Column 2, Lines 10 to 14. It says, Examples of suitable polymers include and then lists suitable polymers from which you can draw or you can go beyond because they are examples of suitable polymers.

And then the next example of materials that are included, examples of

commercially available polymers of this type include. This is Column 2, Lines 22 to Line 50. And these are examples of, obviously, of commercially available polymers.

Next place where materials are considered is example of additives include and hereby have a very long list of things that are examples of additives at Column 2, Line 56 to Column 3, Line 24. Clearly you could go outside of this list, as they are examples.

And then the next one is at Column 3, Lines 57 to 59 where it says examples of such extenders may include and gives examples which clearly you can go outside of in choosing extenders.

If, in summary, the language of antioxidant is selected from. And for me, that is a descriptive list from which you should select. Whereas we have examples of suitable polymers include examples of commercially available polymers include, examples of additives include and examples of extenders include.

So, for me, the language is sufficiently different, but I believe you should

draw only from those antioxidants that are listed in the patent.

Q. So acetaldehyde is an antioxidant. What is your conclusion as to whether the written description requirement is met?

A. I don't believe it is met.

Q. Now, let's turn to indefiniteness. Did you consider the definiteness standard in your analysis?

A. Yes, I did. And that's the slide -- the standard I used. Standard was -- it requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification.

Q. Now, first of all, is there any description in the '031 patent on how to test whether a compound is an antioxidant?

A. There's data, as we have discussed already. There are accelerated stability testing where the active ingredient is included in a pharmaceutical composition with and without an antioxidant. So that there's a method that's described in the patent to help you understand whether you're within the claim.

Q. If the patent is not limited to known antioxidants and standard testing described in the patent, can a person of ordinary skill in the art determine the bounds of the asserted claims?

A. No. I don't believe they can because if you move beyond what is meant to be an antioxidant in the pharmaceutical domain and you move beyond tests that are understood and regarded as standard in the pharmaceutical domain, you move into a range of testing with -- which is essentially unlimited in terms of the kind of conditions you could use and the kind of testing you could apply.

And I don't understand if you get one positive result of those how you would know whether you are within the bounds of the claim in light when read in light of the specification.

Q. If Dr. Davies' study can be used to show that acetaldehyde meets the claim limitation, what is your conclusion as to whether Claim 7 meets the definiteness requirement?

A. My conclusions is that it does not.

Q. Moving on to the enablement requirement. Did you consider the standard for enablement in

your analysis?

A. Yes, I did, and I have a slide for that as well. Standard was that the patent specification teaches those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. And the undue experimentation involves consideration of the following eight factors: Quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in the art, predictability or unpredictability of the art and the breadth of the claims.

Q. Now, did the inventors test all of the antioxidants listed in Column 4, Lines 10 through 15 of the '031 patent?

A. No, they didn't. They tested two of them. They tested alpha tocopherol and ascorbyl palmitate.

And of those two, as we've already heard and discussed, alpha tocopherol worked and ascorbyl palmitate did not work.

Q. Now, if one antioxidant works in a

particular formulation, does that tell you whether a different antioxidant works in that same formulation?

A. No, it doesn't. As I said in my infringement evidence, I think antioxidants are formulation specific.

Q. Now, did the plaintiffs mention anything about whether an antioxidant would work in a particular formulation?

A. Yes, they did. And I have some excerpts from the depositions.

Dr. Theobald, the LTS project manager on Exelon, the question is: So you're saying it was astonishing that an antioxidant would prevent oxidation?

His answer was, It's astonishingly because you can't predict which kind -- I'll skip that -- it's not predictable. You may be successful. You may not be successful.

And it's not predictable which kind of antioxidant is working.

Question: So it's not predictable that an antioxidant stops oxidation?

And the answer is: It's not

predictable that any kind of antioxidant is stopping any kind of oxidation. And he continues, he does not believe it's a predictable outcome.

Second excerpt is from Dr. Theobald. And is his answer on this was: What I'm saying is it's unpredictable in respect to specific API -- specific formulation which antioxidant is going to work.

You can't predict. You have to run a series of experiments in order to find out whether at all and if anyone is doing the job.

So it's clear that Dr. Theobald is saying that there's experimentation that's required to find out whether any antioxidant is going to work in any specific formulation.

The next excerpt is from Dr. Tiemmesen, one of the inventors. And the question is: We talked just a few minutes ago and it's -- Novartis never assessed ascorbic acid, butyl hydroxytoluene, butyl hydroxy anisole, propyl gallate.

How do you know that these antioxidants would have a stabilizing effect on

rivastigmine?

To which he replied, I think it would have to be investigated. So it isn't predictable and requires experimentation in order to see whether the other antioxidants would work and in a particular formulation.

Next excerpt from Dr. Tiemessen is these antioxidants they can be used in a certain set of circumstances for certain compounds, certain formulations to stabilize and to reduce the level of oxidation. But it's not that you can just take one and put it in and it works. That's not the case.

It can even be worse if you add an antioxidant. So this is high level of fine-tuning that's required on that.

It's very clear, Dr. Tiemessen, one of the inventors is saying a lot of experimentation and fine tuning required in order to work out whether an antioxidant is going to be viable for a certain compound, certain circumstances and certain formulations.

The last one is Dr. Ogorka. I'll just read out the highlighted bit, which says,

You cannot predict which antioxidant will be effective. There requires a lot of experimentation to identify the right antioxidant and even more experimentation to establish the adequate level of this.

So, from reading these excerpts from the deposition, I would -- my own view as well is that to understand whether any antioxidant is going to work in any formulation, you have to do what seems to me, at least the amount of experimentation that was done in the patent, in order to demonstrate whether it would be effective.

Q. Did the plaintiffs fail to achieve any embodiments within the scope of the claim?

A. Yes, I believe they did. We talked about alpha tocopherol and ascorbyl palmitate a few moments ago. And I presented the data that alpha tocopherol reduced degradation.

Ascorbyl palmitate reduced the degradants for one a little bit, but didn't reduce the degradation for the other one. So it had failed. And in failing to reduce one degradant is insufficient to produce that product.

Q. Does the patent enable the use of acetaldehyde as an antioxidant?

A. No, it doesn't. I don't think acetaldehyde's in the patent in each of its own list of antioxidants. And to allow acetaldehyde would require the level of experimentation that is talked about in the patent.

Q. What is your conclusion as to whether Claim 7 meets the enablement requirement?

A. The conclusion is that it does not.

MS. KOH: No further questions.

THE COURT: All right. Thank you, Ms. Koh.

All right. Mr. Conde.

CROSS-EXAMINATION

BY MR. CONDE:

Q. Now, Dr. Buckton, you say that the claims of the '031 patent include only the specific antioxidants listed in the specification; right?

A. That's my understanding of the language. And my reading of it is that is true.

Q. That would be your interpretation of the term antioxidant is that it only --

A. No.

Q. -- covers the specific antioxidants in the patent?

A. My reading of the specification of the patent is that's what it says.

Q. Okay. Can we please go to Slide PDX 210?

So, Dr. Buckton, let's compare your definition to the definitions that defendant put forward in this case. And you can see that the defendant put a different definition forward to the Court than yours; right?

A. Yes, I can see that.

Q. So you disagree with defendant's construction?

A. Well, I'm telling you my reading of the patent.

Q. So you disagree with their construction; right?

A. Well, I think it's -- let me read it again. One moment.

I think it's a reasonable construction. I am telling you from the language of the patent how I interpret the patent specification in this context.

Q. So you think the Court's construction is a

reasonable interpretation as well?

A. Obviously, it is the correct interpretation of it. Agent that reduces oxidative degradation.

Q. And, of course, you know that the number of antioxidants that are available to a formulator is much larger than the list that's in the '031 patent; right?

A. I know that I talked about that in my earlier testimony that the list in the excipients handbook, for example, is larger than the list that's in the '031 patent.

Q. And, in fact, the list that's in Modern Pharma Therapeutics, I think I got the name right?

A. Pharmaceutics.

Q. Oh, Pharmaceutics. Thank you.

The list there is longer than in the patent as well; right?

A. I haven't checked that out.

Q. If we go to PDX 211, you see on PDX 211 we've put the example in the '031 patent and the antioxidants listed in Modern Pharmaceutics. And the list is longer in Modern Pharmaceutics;

right?

A. You're quite right.

Q. Now, can we please go to DDX 208, a slide from Dr. Buckton's direct? And you recall you talked about the specification on direct and you pointed to these three portions of the specification; right?

A. That's correct.

Q. And in the very first one, it says in one aspect, a pharmaceutical composition comprising Compound A in free base or acid addition, salt form and an antioxidant. So, in the panel that you cite to, it just says antioxidant in general; right?

A. Within that sentence, it does. The sentence is followed by --

Q. So let's go to the next panel. So the next panel -- the first one was Column 1, Lines 34 to 39.

The next one we're going to look at is Column 4, Lines 5 to 7. And in one of your demonstrative exhibits that you used during your direct, you pointed the Court to this phrase, it says, "In another aspect, the present invention

provides the use of an antioxidant to stabilize a pharmaceutical composition containing Compound A."

Right?

A. That's correct. Yes.

Q. So, again, it used the word antioxidant in general without limitation; right?

A. Well, I think the list of antioxidants is in the same specification and it would be reasonable to use that list within the context of these uses of the words.

Q. It also would be reasonable to interpret an antioxidant broadly to include all of the antioxidants that were in Modern Pharmaceutics and the handbook; right?

A. The decision someone has to make, but I think it's for the Court ultimately to make. But I think the specification lists with peculiar language in the patent that you make only to that list of antioxidants, which to me makes me think that that's the list that it's talking about when it says antioxidant here.

Q. Right. But in other parts of the patent, it doesn't limit antioxidant to any list.

So, one skilled in the art reading these phrases that you use in direct would understand that it's referring to any antioxidant, including those in the textbooks that we've been discussing here today; right?

A. My reading of that definition of antioxidant doesn't, to me, read that it has to be only limited to part of the patent specification. That definition seems to me to read to the whole patent specification.

Q. Now, you agree that the '031 specification provide examples of patches that include an antioxidant; right?

A. The '031?

Q. It provides examples. There's examples, for example, example one includes an antioxidant; right?

A. I can't remember what example one is. Is the patent handy?

Q. Sure. It's in your book. It's PTX 1.

Can we just put example one up on the screen, please? I'm sorry, JTX 1. If we can just put it on the screen.

A. Any way, I've got the patent. Example one

you said? I have it, example one.

Q. And example one includes an antioxidant; right?

A. Example one has alpha tocopherol, so that's correct.

Q. So one skilled in the art would be able to make a transdermal patch within the meaning of Claim 1 using alpha tocopherol; correct?

A. One skilled in the art would be able to make patch --

Q. Yeah. Would be able to make a patch within Claim 1 based on example one of the '031 patent; right?

A. I haven't read around it, but that sounds, on the face of it, quite true. Yes.

Q. I'm sorry, I misspoke. I meant Claim 7.

Same answer to Claim 7?

A. Oh.

Q. The only difference between Claim 1 and 7 is the addition of the secured by a substrate. So one skilled in the art would be able to practice Claim 7 using what is disclosed in Example one; right?

A. It would seem to me that's true.

Q. Now, you agree that one skilled in the art would be able to perform the stress tests that are disclosed in the '031 patent; right?

A. Yes. Sorry.

It's the storing at 60 degrees and the storing at 40 degrees.

Q. And that type of experimentation is routine?

A. Yes.

Q. Now, can we go to Slide DDX 257, which is some of the testimony that you relied on with respect to your opinions. And, again, I'm not going to belabor the point, but for all of these slides, you only put a snippet up. You didn't put up the full amount of testimony that was shown yesterday; right?

A. Just a snippet.

Q. Now, first with regard to this particular snippet, it doesn't even mention Rivastigmine, does it?

A. Within the snippet, it doesn't mention Rivastigmine.

Q. Right. And within the snippet, it doesn't mention whether he's talking about before the

patent was filed or after the patent was filed; right?

A. I agree within the snippet, but I believe that he is talking about Rivastigmine.

Q. But you can't tell whether Dr. Theobald is talking about the period before the patent was filed or after the patent was filed when the inventors discovered the invention of the '031 patent; right?

A. But it doesn't, in this section, give me the filing date. But I -- I believe he's talking about data in relation to the '031 patent.

Q. Data before the patent was filed; right?

A. The data would have been generated before the patent was filed. I -- I don't know how the data could be.

Q. So he's saying it would be astonishing unpredictable prior to the filing of the patent; right?

A. That's not my reading of it at all. My reading is that it's unpredictable after the filing of the patent remaining, so --

Q. But he doesn't say that in this snippet?

A. That's my understanding, very clear

understanding of what he says is he says something that remains true today.

Q. Can we go to the next slide, please. And in this slide again, you don't know whether he's talking about activities before the patent was filed or after the patent was filed; right?

A. I have the same view that this is talking about a situation that remains true now as true as it was whenever he was talking about it, so I regard it as a general statement.

Q. But you don't know from this snippet whether he's talking about the period before the patent was filed or the period after the patent was filed; right?

A. The deposition clearly would have been after the patent was filed and my belief is it is his opinion at that time.

Q. You can't tell whether he was talking about the period before the patent was filed from this snippet; right?

A. I don't see how that would have changed his opinion. I think it's a continuing opinion.

MR. CONDE: I have no further questions, Your Honor.

THE COURT: All right. Thank you.

Any redirect?

MS. KOH: No redirect.

THE COURT: All right. Dr. Buckton, I think we'll try again. You can step down.

THE WITNESS: Thank you very much.

MR. CONDE: Before we put on our next witness, we would respectfully request that we take a lunch break.

THE COURT: I was thinking because really all we got left is Dr. Klibanov; right?

MR. CONDE: Yes, Your Honor.

THE COURT: And he's only addressing invalidity; right?

MR. CONDE: Yes, Your Honor.

THE COURT: And I'm guessing that he probably won't be that long on direct.

MR. CONDE: My understanding, he'll be around an hour, maybe a little less.

THE COURT: In any event, we'll take a break until quarter of 2:00. All right.

(A luncheon recess was taken.)

THE COURT: All right. Please be seated.

Ms. Jacobsen.

MR. JACOBSEN: Your Honor, plaintiffs call Dr. Alexander Klibanov. Dr. Klibanov will be providing testimony on the validity of the '031 patent.

THE CLERK: Please state and spell your full name for the record.

THE WITNESS: Alexander M. Klibanov. A-L-E-X-A-N-D-E-R, Klibanov, K-L-I-B-A-N-O-V.

ALEXANDER M. KLIBANOV, PH.D.,
the deponent herein, having first
been duly sworn on oath, was
examined and testified as follows:

DIRECT EXAMINATION

BY MS. JACOBSEN:

Q. Good afternoon, Dr. Klibanov.

A. Good afternoon.

Q. Can you please state your full name for the record?

A. Alexander M. Klibanov.

MS. JACOBSEN: May I approach, Your Honor?

THE COURT: You may.

BY MS. JACOBSEN:

Q. So Dr. Klibanov, I have given you a book of documents and can you please turn to tab one.

A. Yes.

Q. And there you will find JTX 5A. Do you recognize that document?

A. I do.

Q. What is it?

A. It's my curriculum vitae.

Q. Does it accurately reflect your educational and professional experience?

A. Yes, it does.

Q. Would you please explain why you're here today?

A. Well, I'm here to respond to Professor Buckton's allegations for invalidity of the Claim 7 of the '031 patent. And what I have been asked to do is to review this claim, review the '031 patent, and then determine whether the written description, enablement and definiteness requirements are met by that claim.

Q. Do you feel your experience and training put you in a position to testify on those topics?

A. Yes, I do. I have been working in the

area of pharmaceutical formulations for over forty years. In particular relevant to this case, I have extensive research on oxidations, oxidative degradations, antioxidants including these processes occurring in pharmaceutical formulations including transdermal formulations, so I believe that this experience makes me well qualified to testify here today.

MS. JACOBSEN: Your Honor, plaintiffs offer Dr. Klibanov as an expert in chemistry, pharmaceutical formulations including the use of antioxidants and oxidative degradation.

MR. BROWN: No objection, Your Honor.

THE COURT: All right. You may proceed.

MS. JACOBSEN: Plaintiffs move to introduce JTX 5A, Professor Klibanov's CV into evidence.

THE COURT: I guess without objection.

MR. BROWN: No objection.

BY MS. JACOBSEN:

Q. Professor Klibanov, were you here when Professor Buckton testified?

A. Yes, I was.

Q. And do you agree with Professor Buckton's conclusions with respect to the written description, enablement and definiteness requirements?

A. No, I cannot agree with those opinions.

Q. What did you consider to reach your conclusions?

A. Basically what I did was I asked myself a question, who is a person of ordinary skill in the art in this case, and in particular with respect to Claim 7 for which the date, the parties agree, is January 12, 1998. So then through the eyes of this person, I have determined whether there is clear and convincing evidence that the written description enablement and definiteness requirements are not met with respect to Claim 7. And my answer to this question is there is no such clear and convincing evidence.

Q. In addition to the '031 patent, did you consider any other materials in reaching those

conclusions?

A. Yes. I also have considered the '023 patent. I considered the prosecution histories of both of these patents. I also considered the Court's claim construction.

In addition to that, I also reviewed Professor Buckton's expert reports, obviously what he said in his testimony here, and I also reviewed the excerpts from Novartis' inventors and witnesses, and also the documents from Novartis' testing that Professor Buckton referred to.

Q. Who would be a person of ordinary skill in the art?

A. In my judgment the person of ordinary skill in the art here, the art which deals with pharmaceutical formulations is somebody who would have a doctoral degree in chemistry, pharmacy, or a related field, and two years, approximately, of practical experience in pharmaceutical formulations.

Alternatively, this person could be somebody with a masters degree and about four years of practical experience in pharmaceutical

formulations.

Or this person could be somebody with a bachelors degree in chemistry, pharmacy, or related field with approximately six years of practical experience in pharmaceutical formulations. So I considered the issues and will opine today from the standpoint of such a person.

BY MS. JACOBSEN:

Q. Before we address each of Par's invalidity arguments, what claim is at issue in this case?

A. My understanding is, Your Honor, that the only claim at issue in this case is Claim 7 of the '031 patent.

Q. And can you summarize what Claim 7 of the '031 patent requires?

A. Yes. This Court has seen this claim a couple of times over the last day and a half, so I will be very brief. Essentially, in a nutshell, what Claim 7 of the '031 patent claims is a Rivastigmine transdermal device containing an antioxidant in an amount from about 0.01 to about 0.5 percent by weight.

MS. JACOBSEN: And, for the record, Dr. Klibanov, referred to JTX 1, the '031 patent Claim 7.

BY MS. JACOBSEN:

Q. Dr. Klibanov, are you aware of how the Court has construed the term antioxidant?

A. Yes, I am.

And, in fact, the Court's claim construction of this term is depicted on the screen now. And it says that the term antioxidant is construed to mean agent that reduces oxidative degradation.

MS. JACOBSEN: And for the record, that's DI-250 at Page 1.

BY MS. JACOBSEN:

Q. Does Claim 7 require that the antioxidant provide a stabilizing effect?

A. No, it does not. Claim 7 only, as I understand it, only requires the presence of an antioxidant.

There are no such words as stabilizing, stable, stability or the like in the claimed language of Claim 7.

Q. And with the Court's claim construction in

mind, can we turn to your analysis of the three requirements in question here?

A. Sure.

Q. Written description, enablement and definiteness.

A. Sure.

Q. And let's start with written description.

A. Yes.

Q. What question did you ask with respect to written description?

A. I asked, Your Honor, whether the specification of the '031 patent will reasonably convey to the person of ordinary skill in the art that the inventors were in possession of the invention of Claim 7, which is a Rivastigmine transdermal device containing an antioxidant. That is an agent that reduces oxidative degradation.

Q. Would you explain why Dr. Buckton alleges that Claim 7 does not meet the written description requirement?

A. My understanding of Professor Buckton's position is that Claim 7 -- if Claim 7 includes acetaldehyde within the term antioxidant, then

this claim doesn't meet the written description requirement because it includes antioxidants that are neither listed in the patent specification, nor are established to be antioxidants by any known or recognized method.

Q. Do you agree?

A. No, I do not agree. And the reason that I don't is illustrated on this slide.

These, Your Honor, are two excerpts from the '031 patent from Column 1. The first one says and I quote, "It has now been found after exhaustive testing that Rivastigmine is susceptible to degradation, particularly in the presence of oxygen."

The second excerpt says, "In one aspect, the invention provides a pharmaceutical composition comprising Rivastigmine and an antioxidant."

So, in my opinion, one of skill in the art having reviewed, for example, these excerpts will understand that the inventors of the '031 patent made at least two discoveries. First discovery is that they found that Rivastigmine is susceptible to oxidative

degradation. The second is they discovered a Rivastigmine transdermal device or Rivastigmine pharmaceutical composition in general which contains an antioxidant.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 1, the '031 patent at Column 1, Lines 22 to 24 and 34 to 36.

BY MS. JACOBSEN:

Q. Is the term antioxidant limited to specific antioxidants?

A. No, in my opinion, it isn't.

Your Honor, at the time in 1998, there were a lot of different antioxidants known. And it is clear that the specification of the patent doesn't attempt to list them all.

Rather, the specification of the patent gives some examples of different types of oxidizing agents or I'm sorry, different types of antioxidants.

So, as the Court has heard, for example, ascorbyl palmitate and ascorbic acid are examples of antioxidants that act by working as reducing agents. In contrast, for example, butyl hydroxytoluene, also known as BHT is another

antioxidant, but it acts via a different mechanism, namely by working as a free radical scavenger.

So, one of skill in the art, would understand that this is not an exhaustive or limiting list, but rather, these are just some examples of certain types of antioxidants.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 1, the '031 patent at Column 4, Lines 11 to 16.

BY MS. JACOBSEN:

Q. Dr. Klibanov, is there any other evidence that the term antioxidant wouldn't be limited?

A. Yes, there is. In fact, the plain language of in this case, claims of the '023 patent reveals that as well. So these are the first three claims of the '023 patent. The first and the broadest claim, Claim 1, uses the term antioxidant. The second claim and the third claim are both dependent from Claim 1, either directly or indirectly, and these two dependent claims, two and three, list all the same antioxidants as were listed in the specification of the patent.

So one of skill in the art would understand, therefore, that the term antioxidant as it is used in Claim 1, must be broader than just the list that is provided in the specification of the patent because these two claims, two and three, are dependent from Claim 1, and therefore antioxidant, the antioxidant term in Claim 1 must include other antioxidants as well.

Q. Was the meaning of antioxidant in the '023 patent relevant to the meaning of antioxidant in the '031 patent?

A. Yes, in my opinion very much so. Because as this Court knows, the '023 and '031 patents are sister patents, they share essentially the same specification. My understanding is that the claims must be read in light of the specification. And, therefore, the term antioxidant, the claim term antioxidant in Claim 1 of the '023 patent must be read exactly the same way as the claim term antioxidant in Claim 7 of the '031 patent, which is at issue here.

MS. JACOBSEN: For the record, Professor Klibanov referred to JTX 2, the '023

patent, Claims 1, 2 and 3. And Your Honor, I don't believe that the '023 patent is in evidence, so we move to introduce JTX 2, the '023 patent.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. And why does Dr. Buckton argue that the term antioxidant is more limited?

A. Well, my understanding of Professor Buckton's position is that he focuses on the particular expression found in column four of the '031 patent, and specifically where it says that stabilizing effect, that an effective, stabilizing effect is surprisingly achieved when the antioxidant is selected from, and from the basis of this phrase, selected from, Dr. Buckton concludes that the antioxidants within this invention must be limited to only those that are listed here.

Q. And for the record, Dr. Klibanov referred to JTX 1 at column four, lines 11 to 16.

Dr. Klibanov, do you agree with

Dr. Buckton's reading of this passage?

A. I do not agree. I don't believe that one of skill in the art would read this passage in the way so limited. Instead, one of skill in the art would readily understand the Court's claim construction of the term antioxidant, which is an agent that reduces oxidative degradation, and therefore, will understand that any agent that reduces oxidative degradation could be used as an antioxidant with these being just examples.

Q. And do you agree that Claim 7 includes compounds not demonstrated to function as antioxidants by any established testing method?

A. No, I do not agree with that, either, because again, this is an excerpt from the '031 patent that this Court has seen already over the last day-and-a-half, and it says specifically, "The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests."

So this specifically says to one of skill in the art that if he or she wanted to see whether there is a reduction in degradation, oxidative degradation by-products, for example,

this person could employ stress stability tests that also have been discussed extensively in this courtroom over the last day-and-a-half and then use the stability test as an example to ascertain that.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 1, the '031 patent, column one, lines 37 to 39.

BY MS. JACOBSEN:

Q. Dr. Klibanov, did you understand Dr. Buckton to rely on any other evidence in support of his opinion that the '031 patent does not meet the written description requirement?

A. No, my understanding was there was no other evidence that Professor Buckton relied upon.

Q. So would you please summarize your conclusions on written description?

A. Yes. My conclusion is that one of skill in the art reading the specification of the '031 patent will understand that the inventors were in possession of the invention of Claim 7, which is a rivastigmine transdermal device containing an antioxidant, with an antioxidant being an agent

that reduces oxidative degradation.

Q. Let's turn now to enablement. What question did you ask with respect to enablement?

A. The question

A. The question that I asked is whether one of ordinary skill in the art would be able to practice the invention of Claim 7, that creates a trans -- a Rivastigmine transdermal device containing an antioxidant based on this person's own knowledge in combination with the teachings of the specification of the '031 patent.

And my answer to this question is, yes, one of skill in the art will be able to do it.

Q. And would they have been able to do it without undue experimentation?

A. They would be able to do it without undue experimentation, yes.

Q. And how did you reach that conclusion?

A. Well, I reached that conclusion by analyzing the language of Claim 7, by analyzing the specifications of the '031 and '023 patent, by analyzing what one of skill in the art would have known at the time and, of course, in light

of the Court's claim construction.

Q. Would you please summarize your understanding of Dr. Buckton's non-enablement argument?

A. My understanding, Your Honor, is that Professor Buckton believes that the written -- that the enablement requirement is not met for two reasons.

The first reason is that, in Professor Buckton's opinion, one of the antioxidants tested by Novartis ostensibly didn't work. In fact, today he broadened it to say that two of the antioxidants tested didn't work. So that's the first reason.

And the second reason, as I understand it, is that Professor Buckton believes that if acetaldehyde is included within the term antioxidant in Claim 7, then testing will necessarily be required.

Q. I'd like to start with the first of those reasons. In your analysis, did you consider plaintiff's testing with ascorbyl palmitate?

A. Yes.

Q. And can you please turn to Tab 6 in your

witness binder, and there you should find JTX 182.

A. Yes.

Q. Do you recognize this document?

A. I do.

Q. What do you recognize it to be?

A. These are LTS -- this is an LTS letter that was forwarded to Novartis which presents some stability testing studies.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce into evidence JTX 182.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. And do you agree with Dr. Buckton that ascorbyl palmitate didn't work?

A. No. I do not agree with that. And, Your Honor, you've heard several times today that ascorbyl palmitate didn't work and Professor Buckton also added that the combination of ascorbyl palmitate and tocopherol didn't work.

So I feel that perhaps it would be

worthwhile to take sort of a deeper look into what these data are and what they say and don't say. So these are Novartis' data that address the issue of formation of degradation products of Rivastigmine base in the presence of antioxidants after eight weeks storage at 60 degrees.

And what we have here is the results of four head-to-head tests. These are stress tests and the stress was temperature of 60 degrees and the test time of eight weeks.

Now, the Court has heard over the last day and a half several times that when Rivastigmine undergoes degradation, oxidative degradation, there are two oxidative degradation products that are formed. They are the ketone product and the styrene product.

These are the data that Dr. Buckton showed. So let's take a look at these data.

The first entry in this table is Rivastigmine alone. No antioxidant.

This is called formulation 2200. And Your Honor can see that after eight weeks at 60 degrees Centigrade, there is a significant

amount of the ketone product, of the styrene products and the total amount of the oxidative degradation product exceeds five percent. So that is what happens in the absence of antioxidants.

Next thing that's reported in this table this, is the second entry is the same formulation with the only difference that 0.1 percent tocopherol is also present. The Court can see that the total, and the total column is the one that I added that are added by simply summing up the ketone oxidative product and the styrene oxidative product.

The Court can see that the total amount of oxidative products is greatly reduced by a factor of approximately five. Okay.

So tocopherol obviously greatly reduces oxidative degradation. The second entry -- the third entry is what Professor Buckton opined showed that ascorbyl palmitate didn't work.

Well, if we look at the data, so this is the amount of the ketone formed. This is the amount of the styrene formed, I summed them

up. And the Court can see in blue here that the total amount of oxidative degradation products is 3.6 percent, which is about one-third less than in the case of rivastigmine without an antioxidant.

Likewise, in the case of rivastigmine containing a combination of ascorbyl palmitate and tocopherol, as opposed to tocopherol alone, we can see that the total amount of degradation products, oxidative degradation products is about 2.79, so we have roughly a twofold reduction in the total amount of degradation products.

So if we now review this data and analyze them. What do we see? Well, we see several things. First of all, we see that with each of these antioxidants and the combination of these antioxidants we have a significant reduction in the total number of oxidation products.

We can also see that tocopherol is unquestionably the most potent antioxidant here.

However, we can also see that ascorbyl palmitate, although not as potent as

tocopherol, also reduces the total number of oxidation products as I mentioned a moment ago by about thirty percent.

So there is no question -- and the combination of ascorbyl palmitate and tocopherol affords an even greater reduction in oxidation products.

So there is no question in my mind, and I think that's how one of skill in the art would also analyze this data that all three antioxidants presented here in these head-to-head tests in fact afforded a significant stabilization, significant reduction in oxidation of rivastigmine in this instance.

Q. Dr. Klibanov, the comparison that you made between the formulation, the comparison you made with the combination of two antioxidants, and I believe you said it caused a twofold reduction, that was relative to no antioxidant?

A. Yes. We compare everything with respect to no antioxidant present, yes.

Q. And why did you consider the total amount of degradation by-products?

A. Well, the reason, Your Honor, I consider

the total amount is because the key question here is how much rivastigmine has been lost to oxidative degradation. Well, that rivastigmine that has been lost to oxidative degradation, where did it go?

Well, it has gone either in the ketone product or into the styrene product. Therefore, if one wants to assess how much rivastigmine has been lost to oxidative degradation, I think it's fairly straightforward that one simply has to take the sum of these two products, rather than just one product, either this one or this one. That is why from a purely scientific standpoint I think that it's very clear that one has to take the sum of the oxidative degradation products.

I just want to say that this rationale is also confirmed by the specification of the patent.

MS. JACOBSEN: And we'll look at that in just a second.

For the record, Dr. Klibanov referred to JTX 182 at page 24880.

BY MS. JACOBSEN:

Q. You said that was consistent with the patent?

A. Yes. This scientific rationale, Your Honor, is also confirmed by the plain language of the specification of the patent.

For instance, there are three excerpts here on the screen now. The first one says, "The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests."

I want to emphasize that it was degradation by-products, plural, not one degradation product, but degradation by-products plural. It does so again in the next excerpt where it does it repeatedly, it says twice degradation products. And then, degradation products, again, plural.

Finally, in the third excerpt, it says insignificant amounts of degradation products are detected after storage of at least four months at room temperature. And once again, the inventors used plural, degradation products, which confirms the scientific rationale that I explained a moment ago.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 1, the '031 patent at column one, lines 37 to 39, column four, lines 20 to 25, and column seven, lines 40 to 52.

BY MS. JACOBSEN:

Q. If we could just put up the slide again with the results. Do you agree with Dr. Buckton that the increase in the amount of styrene product shows that ascorbyl palmitate didn't work?

A. No, I cannot agree with that because as I said, if you wish to assess how much rivastigmine has undergone oxidative degradation, you must take the sum of the ketone oxidative degradation product and the styrene oxidative degradation product. Which product predominates in the resulting mixture in my opinion is not relevant to the question of how much rivastigmine has undergone oxidative degradation.

Q. Dr. Klibanov, how much ascorbyl palmitate was tested in this experiment?

A. Well, the Court can see that the amount of ascorbyl palmitate that was tested here is 0.1 percent. And the significance of this number is

that the Court will recall that Claim 7 of the '031 patent allows up to about 0.5 percent of antioxidant.

So even if we put aside the word "about" just based on 0.5 percent alone, one of skill in the art would understand that the amount of ascorbyl palmitate that could be used was five times greater than that. In other words, one could use 0.5 percent ascorbyl palmitate.

A. In other words, one could use 0.5 percent ascorbyl palmitate. If one were to use a larger amount of ascorbyl palmitate, obviously, it will have a greater reducing power; and therefore, one of skill in the art would conclude that it is likely that at 0.5 percent, ascorbyl palmitate will be even more effective than at 0.1 percent.

However, I still want to emphasize that even 0.1 percent shown here, a clear comparison of 3.6 percent of degradation products for the ascorbyl palmitate experiment and over five percent for Rivastigmine alone experiment indicates that even 0.1 percent ascorbyl palmitate is a significant -- affords a significant reduction in oxidative degradation

and; therefore, in my opinion, is clearly an antioxidant.

MS. JACOBSEN: And for the record, again, Dr. Klibanov referred to JTX 182 at Page 24880.

BY MS. JACOBSEN:

Q. Dr. Klibanov, did LTS record any conclusions from these tests?

A. Yes, they did. So in the LTS document that we're discussing, they asserted after they presented the data in the tabular form and the bar chart form, they stated from these experiments it could be concluded that tocopherol seemed to be the most powerful -- emphasis added -- antioxidant in order to reduce the formation of ENA degradation products in the TDS.

With the ENA being Rivastigmine, Your Honor, and TDS being a transdermal device or transdermal system. So, reading this sentence, one will understand that what they said here, we should -- which is consistent with what we just concluded a moment ago, is that tocopherol was the most powerful antioxidant.

They certainly didn't conclude that

ascorbyl palmitate was not a suitable antioxidant or was not an antioxidant. Nor did they conclude that either combination of tocopherol and ascorbyl palmitate or another compound could not be an antioxidant as well.

Q. In your analysis, did you consider any inventor and witness deposition testimony?

A. Yes, I did.

Q. And did any of that testimony change your opinion?

A. No, it didn't. And, Your Honor, you heard yesterday you heard some deposition testimony played, and today Professor Buckton presented some excerpts. The reason they didn't change my opinion is that the way I understood that deposition testimony in particular, when read beyond a snippet that was shown on the screen, was that those folks were talking about either a commercial device, a commercial transdermal device and we're discussing commercial marketing-type issues in terms of what antioxidant will be the most suitable.

And in this context concluded that tocopherol was the most suitable, which is hard

to disagree with. On the basis of the test data we just reviewed or some other Novartis personnel, including the inventor, they were discussing what would or would not have been known without the benefit of the invention of the '031 patent, which in my opinion, as I understand it, is not probative to the 112 issues of invalidity.

Q. And why is it your understanding that that's not probative to the 112 issues?

A. Because these issues require that one of skill in the art relies not only on his or her own knowledge, but also has the benefit or the teachings of the invention of the patent. And, of course, one couldn't have the benefit of the teachings of the invention of the patent before the patent.

Q. And was the deposition testimony that you considered the same as the deposition testimony played in Court yesterday?

A. Yes, it was.

Q. So I'd like to turn now to the second reason that Dr. Buckton says that the '031 patent is not enabled. And in your analysis, did you consider whether a person of ordinary skill in the

art would have had to test to determine whether a compound reduced oxidative degradation?

A. Yes, I did consider that.

Q. And what did you conclude?

A. Well, my conclusion was that that is not necessarily the case. For example, with respect to these compounds that are listed in Column 4, things like tocopherol, esters thereof, ascorbyl palmitate and others, no testing was required. The inventors told one of skill in the art that they can be used.

One could also go to -- one of skill in the art could also go to prior art literature and find some other antioxidants that could be used. Or alternatively, one could also conduct experimentation, experimentation which, as I already mentioned, is not undue or one could use some kind of a combination of, for example, prior literature, prior art literature and the experimentation. So experimentation is not definitely required.

MS. JACOBSEN: And for the record, Dr. Klibanov was referring to JTX 1, the '031 patent, Column 4, Lines 11 to 16.

BY MS. JACOBSEN:

Q. Does the '031 patent provide any guidance on the testing that can be used to determine whether a compound is an antioxidant?

A. Yes, it does. And, in fact, I showed this excerpt to the Court a few minutes ago. And it says the pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests.

So one of skill in the art learns from that that, for example, he or she could use stress stability tests to see whether there's a reduction in oxidative degradation products. And, indeed, two examples of the specific examples of such testing are, indeed, shown in Column 4 of the specification of the patent.

Q. And can you describe those examples for me?

A. Sure.

So this is the first example, both of these, Your Honor, were stress to stress -- I'm sorry, head-to-head tests and they were both stress tests. In the first one, the stress was 60 degrees, and the time was two months.

And the Court can see that in these head-to-head experiments, basically there are two samples, one a controlled sample that only has an -- that only has a rivastigmine, no antioxidant. The second sample is everything the same except that in this case it had 0.1 percent tocopherol, the antioxidant.

And the Court can see that without an antioxidant, there was about -- there was a 4.46 percent amount of oxidative degradation products, whereas with the antioxidant, there was only 1.3 percent.

So there was roughly a three-and-a-half fold reduction in the total number of degradation products. So tocopherol indeed reduced the oxidative degradation.

Likewise, in the second test which was carried out under different conditions, so here we have 40 degrees, not 60, 75 percent relative humidity, three months rather than two months, and a different concentration of the tocopherol.

But again, in the controlled sample which is rivastigmine with no antioxidant, we

have 1.09 percent oxidative degradation products, whereas in the presence of 0.15 percent of tocopherol, we have 0.25 percent degradation products, so in other words four times less.

So once again, we can see that in these head-to-head tests, regardless of what conditions, set of conditions was used, this one or this one, we see that a significant stabilization against or significant reduction in oxidative degradation was achieved.

There is another important lesson to be learned, Your Honor, from these examples that are provided in the patent. In addition to the fact that you have to run head-to-head tests where there is only one variable between the two samples, namely the presence or the absence of the antioxidants. Another important lesson is --

MR. BROWN: Your Honor, we object to this testimony as beyond the scope of Dr. Klibanov's expert reports. He didn't testify about any opinions in his expert reports about the proper testing being conducted, the necessity for head-to-head testing, anything like that.

THE COURT: Ms. Jacobsen.

MS. JACOBSEN: Two responses to that. The first is that Dr. Klibanov is responding to the enablement argument that there are tests disclosed in the '031 patent that would enable a person of ordinary skill in the art to identify an agent that reduces oxidative degradation. And Dr. Klibanov explained in his report that these tests are examples of the kind of tests that can be done.

And second, Dr. Buckton went beyond his reports and we raised this issue at the pretrial conference and Your Honor said that Dr. Klibanov could respond to the extent that the infringement arguments are now coming into the 112 issues and that's also what Dr. Klibanov is doing here.

MR. BROWN: Your Honor, Dr. Buckton, I believe did not go beyond his expert reports at all. The invalidity section was by plaintiff's request segregated off. He testified very closely and carefully to what was in his reports. I didn't hear any objections from plaintiffs that he went beyond his expert reports.

THE COURT: At the pretrial

conference as I remember what Ms. Jacobsen said, maybe not a hundred percent of it, there was something where I said that Dr. Klibanov could go beyond. I think it was Dr. Buckton, not that he had gone beyond, but he did use a supplemental report. Right?

MR. BROWN: Your Honor as I recall that was not the case, as I recall what happened was plaintiffs were supposing that Dr. Buckton might go beyond his expert reports at the time. Dr. Buckton did not provide a supplemental expert report. They were relying on our response to their motion in liminae in which we identified other evidence including other portions of Dr. Buckton's testimony that we thought was relevant to the issue of the 112, and they were concerned that in 112 testimony, he would go beyond his expert reports. He did not. He provided testimony very much in line with what was in his expert reports.

And Dr. Klibanov is now going far beyond what he provided in his expert reports. And I also believe during the pretrial conference in that ruling, the Court noted that you were

sure that Dr. Klibanov in formulating his opinions had read our entire reports.

THE COURT: I'm still sure of that.

MR. BROWN: And that I believe that your comment was limited entirely to the situation if Dr. Buckton went beyond his expert reports and his testimony about 112.

THE COURT: Anything further, Ms. Jacobsen?

MS. JACOBSEN: Yes. One of the first answers in Dr. Buckton's 112 section was for all the reasons I explained during my infringement, acetaldehyde is not an antioxidant. And it seems clear that Par is planning to import his infringement opinions into their validity case in posttrial briefing and trying to bring in the noninfringement elements into 112 even though maybe on the stand Dr. Buckton didn't specifically address or reiterate all of his noninfringement opinions

MR. BROWN: What we asserted, post-trial briefing, Par argues an entirely different matter than what Dr. Buckton testified.

THE COURT: Well, actually I think I think Ms. Jacobsen's last response indicated to me that, in fact, Dr. Buckton really hadn't gone beyond what was in his reports. And I don't think -- I haven't heard so far anything about what he said during his infringement testimony that's going to add weight or significance to anything that he said during his invalidity testimony.

So I'm going to sustain the objection.

BY MS. JACOBSEN:

Q. So, Dr. Klibanov, would you summarize your conclusions on enablement?

A. Having conducted the analysis that I've just discussed, I concluded that one of skill in the art when he or she uses a combination of his or her own knowledge, and what the inventors discovered and conveyed to one of skill in the art in Claim 7 of the '031 patent using the -- when read in light of the specification, would conclude that the inventors would conclude that one of skill in the art could practice the invention of the '031 or the Claim 7 of the '031

patent, namely could make Rivastigmine transdermal device without undue experimentation. And, therefore, this claim meets the enablement requirement.

Q. And, Dr. Klibanov, you referred to the stress tests that are mentioned in the patent. Would it have taken undue experimentation to run a stress test to determine whether an agent reduces oxidative degradation?

A. In my opinion, it wouldn't because one simply could repeat what was done by and reported by the inventors in the specification.

Q. And is a stress test standard in the pharmaceutical industry?

A. They are very standard and they're used routinely to determine the extent of oxidative degradation and the effect of antioxidants on that oxidative degradation.

Q. And are the examples in the patent the only way to conduct stress tests?

A. No, these are just examples. I mean, there are no standard universal ways to conduct these tests. These are just examples, good examples. But there are others as well.

Q. Dr. Klibanov, did you provide testimony about the non-obviousness of the claims of the '031 patent during the Watson trial?

A. Yes, I did.

Q. And when you analyzed whether the '031 patent was obvious, did you consider what was taught in the '031 patent?

A. No. For that analysis, I did not because my understanding of the law from the counsel here, Your Honor, is that in analyzing obviousness or non-obviousness, one has to consider only what one of skill in the art would have known without the benefit of the invention in question.

Whereas for the enablement analysis and for the enablement analysis, my understanding is that one has to take into account not only a person of ordinary skill in the art's own knowledge, but also the discoveries made in the patent.

In other words, a person of ordinary skill in the art relies not only on the prior art literature, but also has the benefit of the invention of the patent-in-suit.

Q. And was that significant to your analysis?

A. It is very significant because, as I mentioned earlier, the inventors made several discoveries and described in the patent, including the fact that Rivastigmine is subject to oxidative degradation.

That wasn't known before and including a Rivastigmine transdermal device containing an antioxidant, among others.

Q. Thank you.

Dr. Klibanov, finally, let's turn to definiteness. What question did you ask with regard to definiteness?

A. Well, I asked a question whether a person of ordinary skill in the art would understand the boundaries of the claim term antioxidant within Claim 7 of the '031 patent.

And if so, then the definiteness requirement is met.

Q. And why does Dr. Buckton allege that Claim 7 of the '031 patent is indefinite?

A. My understanding of Professor Buckton's position is that he believes that if acetaldehyde is included within the term, claim term

antioxidant of Claim 7, then one of skill in the art, this person will not know the scope of Claim 7; and therefore, will not be able to understand this claim term and the claim as a result.

Q. Do you agree?

A. I do not agree. No.

Q. And why not?

A. I do not agree because I believe that one of skill in the art would be able to clearly understand the Court's claim construction. That is, antioxidant is an agent that reduces oxidative degradation.

And then, for example, using the teachings of the specification of the patent, will be able to readily ascertain what agent is and what agent is not one that reduces oxidative degradation; and therefore, is or is not an antioxidant.

Q. And how would a person of ordinary skill in the art determine that?

A. Well, a person of ordinary skill in the art has several options. The person of ordinary skill in the art could rely on the list that is provided in the -- in column four of the patent,

or one could go to the literature, or one could conduct a straightforward testing or use some kind of a combination of the three.

Q. Does the '031 patent provide any guidance as to the testing that can be used?

A. It does. As already discussed a little earlier, it says, for example, the pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability test. And then it provides an example of both an execution of such a test and the results obtained in such a test.

MS. JACOBSEN: For the record, Dr. Klibanov referred to the '031 patent, JTX 1, column one, lines 37 to 39.

Q. Dr. Klibanov, is there any evidence that different stress tests would yield different or inconsistent results?

MR. BROWN: Objection, Your Honor. This is no where in his expert reports.

MS. JACOBSEN: Your Honor, this is responding to Dr. Buckton's argument that the results of Par's stability data is inconsistent with the results of Dr. Davies' stress test, and

that goes to the definiteness 112 analysis.

THE COURT: Hold on a second. I'm sorry, Mr. Brown, your objection is that this is not in his report?

MR. BROWN: This is not in his expert report.

THE COURT: And Ms. Jacobsen, is it in his expert report.

MS. JACOBSEN: It's not, but it's responding to a new argument that Par has raised at trial. If Par is no longer advancing the argument that there are inconsistent results between Par's stability data and Dr. Davies' stress test data, then obviously we don't need this testimony, but it's a 112 issue and Dr. Klibanov is opining on the validity issues.

MR. BROWN: Again, Your Honor, they're mixing and matching the difference between what Par is asserting and what Dr. Buckton testified. Dr. Buckton never testified regarding the specific conflict between those two tests, and there wasn't any.

THE COURT: Would you agree, Ms. Jacobsen, that Dr. Buckton didn't testify

that there was any conflict between these two tests?

MS. JACOBSEN: I do disagree, Your Honor. Dr. Buckton testified that Dr. Davies' stress test does not show that acetaldehyde is an antioxidant and he testified that Par's stability data shows -- sorry, I think I may have said that the wrong way around, that Dr. Buckton testified that Dr. Davies' stress test did not show that acetaldehyde is an antioxidant, and if it did --

THE COURT: I remember that.

MS. JACOBSEN: -- then it's consistent with Par's stability data which shows that it is not.

THE COURT: Hold on a minute.

All right. So my law clerk remembered hearing that. If you want to pursue it, what I would like to do is get the court reporters, because I don't think it will take very long, to actually go and get me what was said during the indefinite portion of the testimony. Is that when you're saying it was said?

MS. JACOBSEN: Your Honor, maybe a

shorter way of dealing with it is if Par can say whether or not they're going to rely on an allegation of inconsistent results between different tests and then if they're not, and they're not advancing that argument, then we don't need to respond to it and we can leave it there.

THE COURT: All right. I think I know what Mr. Brown is going to say. Mr. Brown, what are you going to say?

MR. BROWN: I'm going to say what we argued is very distinct from what Dr. Buckton testified. We can rely on Dr. Davies' test to support it, we can rely on Dr. Buckton testified very closely, carefully what was in the expert reports, he did not provide any new opinions, and we object to that.

THE COURT: So I'm going to sustain the objection, more or less for the same reason as before, which is I accept what Dr. Buckton said, among other things there was an objection to what was in his expert reports, and I believe it is the case that without saying Dr. Klibanov put this in his reports, so since Dr. Buckton

didn't do beyond the scope of his, I don't think Dr. Klibanov should go beyond the scope of his. And as a practical matter it's unlikely that I'm going to be very impressed by tying things together with no expert to tie it together.

MS. JACOBSEN: Thank you, Your Honor.

BY MS. JACOBSEN:

Q. In which case, Dr. Klibanov, can you summarize your conclusions on definiteness?

A. Well, my conclusion is that one of skill in the art in my judgment having reviewed the claim language, having read it in light of the specification, and relying on his or her own knowledge from the prior art will be able to understand the scope of Claim 7 of the '031 patent, and therefore, that claim as I understand it, as I understand the patent law, meets the definiteness requirement.

MS. JACOBSEN: Just one second. Your Honor.

We have no further questions at this time.

THE COURT: Before you sit down, Dr. Klibanov, let me ask you a question. I'm not sure this is actually a relevant question, but I would like to know what your opinion about it is. Is would a person of ordinary skill in the art at the relevant time, 1998, have understood the term antioxidant to include acetaldehyde?

THE WITNESS: In my opinion, yes.

THE COURT: And why is that?

THE WITNESS: In my opinion, yes.

THE COURT: And why is that?

THE WITNESS: Because acetaldehyde is a reducing agent and therefore, it is akin to such expressly exemplified reducing agents as ascorbic acid or ascorbyl palmitate. So it has, just like those compounds, it has the ability to reduce oxidizing species and there can act as an antioxidant.

THE COURT: So the things like -- and I don't have the exact terminology like the pharmaceutical handbooks that have lists of antioxidants and it's not there. What's your explanation for that?

THE WITNESS: Well, what you have in

the pharmaceutical handbooks are some of the most popular well-established antioxidants. Certainly not all known antioxidants are included there.

And what they list are just some particular antioxidants that have been used in pharmaceutical products prior to that.

THE COURT: All right. So Ms. Jacobsen if that inspires any other questions on your part. Go ahead.

Otherwise, I have no more questions.

MS. JACOBSEN: I have no more questions, either, Your Honor.

MR. BROWN: Your Honor this is a little difficult to do, but I want to move to strike all of Dr. Klibanov's testimony in response to the Court's questions. Dr. Ganem, in this case, produced expert reports expressly addressing the issue of acetaldehyde was an antioxidant.

Dr. Klibanov did not respond. At no point in this time did Dr. Klibanov offer any expert reports or -- actually Dr. Klibanov is nodding no. He did respond to narrow issues that Dr. Ganem raised, but it's then been moved out of

the case.

At no point in the case does Dr. Klibanov in any of his expert reports or otherwise offer that acetaldehyde was an antioxidant. At no point did Dr. Klibanov ever offer an opinion that Par's product infringed.

And we think it's very prejudicial to let on to the record new testimony and new evidence from Dr. Klibanov that we have not had the opportunity to go through discovery and take depositions on.

THE COURT: There may be some merit to what you say. Ms. Jacobsen.

MS. JACOBSEN: Your Honor, you were asking those questions in the context of the 112 analysis and that's exactly what Dr. Klibanov has opined on and put in his expert reports.

THE COURT: Well, I'll tell you what, I will take the motion to strike under advisement. I will grant it unless there's or what I'm inclined to do is I will grant it, unless in the post-trial phase, Novartis produces a copy of the expert report where he said this. Because, your right, Mr. Brown is he hasn't said

this before.

MR. BROWN: Yes, that's correct.

THE COURT: All right. So if he said it before, it will stand. And if he hasn't said it before, I'll strike it.

Okay?

MS. JACOBSEN: Okay. Well, he has responded saying that even if the patent is infringed, it's still valid and that doesn't extend the scope of the term antioxidant. It doesn't make it indefinite or invalid for written description or lack of enablement.

THE COURT: Okay. You're saying he and you're looking in Mr. Brown's direction. You are still talking about Dr. Klibanov?

MS. JACOBSEN: No, I'm sorry. Dr. Klibanov in his expert report has respond to the argument that even if the patent is infringed, it is still valid.

And that is --

THE COURT: My question was did he say in his expert report that a person of ordinary skill in the art would have understood acetaldehyde to be an antioxidant.

MS. JACOBSEN: I'm not sure if that's in his reports.

MR. BROWN: Your Honor, I'm quite sure it's not.

THE COURT: I'm kind of guessing now that probably it's not because I imagine if I hadn't asked that -- well, I imagine you would have asked what the answer was.

All right. Well, I will take it under advisement, but I will probably grant your motion, Mr. Brown.

So, go ahead.

BY MR. BROWN:

Q. Good afternoon, Dr. Klibanov.

A. Good afternoon.

Q. I'm Dan Brown. We met at your deposition.

I'm going to ask you a few questions on behalf of Par. Dr. Klibanov, in addition to being an expert in the current litigation, you were also serving as an expert for Novartis in another litigation pending in this Court against two defendants, Alvogen and Noven; is that correct?

A. I -- definitely, yes, with respect to

Noven. Alvogen, I'm not sure.

It's possible. I just don't remember.

Q. Noven's good enough. And in that case, you've submitted declarations in support of claim construction; correct?

A. Yes.

Q. And in that case, Novartis is arguing for the same claim construction of antioxidant that is in this case; correct?

A. Yes.

Q. And in support of that claim construction and your opinions in that case, you have given the opinion, have you not, that there is a class of compounds known in the art as antioxidants based on their generalized ability to reduce oxidative degradation?

A. I need to take a look at it. I don't remember.

Q. Well --

A. If you tell me that that's what I said, I'll take your word for it.

Q. Let me just ask your opinion. Do you believe that there is a class of compounds known

in the art as antioxidants based on their generalized ability to reduce oxidative degradation?

A. I think it's a reasonable statement. It depends on the context, but it's a reasonable statement. Yes.

Q. And do you have an understanding as to what the term generalized means?

A. Could you please read the entire quote again.

Q. There is a class of compounds known in the art as antioxidants based on their generalized ability to reduce oxidative degradation.

A. It means that, regardless of the mechanism of action, they have the ability to reduce oxidative degradation. Indeed, as I explained during my direct testimony, some of them act as a reducing agent. Some of them act as free radical scavengers.

So, regardless of the mechanism, they reduce oxidative degradation.

Q. Now, Dr. Klibanov, it's your opinion that an antioxidant may react chemically with a drug that is intended to stabilize; correct?

A. It's possible.

Q. And, in fact, it's your opinion that an antioxidant could increase drug degradation; correct?

A. It's possible, if it reacts unfavorably then that's a possibility.

Q. And could I go back to slide ten from your slide deck and you walked through this at length on your direct examination. I just want to do a comparison between now the second formulation, 2200 plus .1 percent tocopherol, and the fourth formulation, no, it's the one above that, 2200 plus .1 percent tocopherol, and 2200 plus .1 percent ascorbyl palmitate, plus .1 percent tocopherol?

A. Yes.

Q. Now, Doctor, the only difference between these two formulations is the addition of .1 percent ascorbyl palmitate; correct?

A. That's correct.

Q. And the difference between total degradation of products here caused by the addition of the .1 percent ascorbyl palmitate is an increase of between two and three times the

amount of total degradation products; correct?

A. That's right.

Q. If someone came to you with just these two sets of data, would this demonstrate to you that ascorbyl palmitate is not an antioxidant?

A. No, it won't. What it would demonstrate to me that ascorbyl palmitate just like I mentioned earlier, an excipient can unfavorably react with the pharmaceutical, an excipient also unfavorably reacts with another excipient. What it would tell me is ascorbyl palmitate unfavorably reacts with tocopherol, thereby reducing tocopherol's ability to reduce oxidative degradation.

Q. Thank you, Doctor.

I would like to now show you another document?

MR. BROWN: May I approach, Your Honor?

THE COURT: Yes.

BY MR. BROWN:

Q. This exhibit is JTX 91. I just want to go to the very last page, or excuse me, I don't think it's the last page, page 123 of the

reference where they're reporting their conclusions. And this is something that we looked at in testimony of Dr. Davies.

I would like to highlight the sentence starting with the word surprisingly, and I'll read it into the record. "Surprisingly the core containing BHT at a concentration equivalent to the 2.0 percent BHT coating had higher levels of the sulfoxide degradant. Due to the instability of BHT and the stability of the BHT radical species, BHT radicals can enhance the oxidation in the core."

Dr. Klibanov, you provided infringement testimony in the Watson trial that BHT is an antioxidant; correct?

A. That's right.

Q. Now, if someone came to you and we assume that the researchers in this publication are correct and came to you with this evidence that in this instance it enhanced the oxidation in the core of their formulation, would that make you change your opinion and conclude that BHT was not an antioxidant?

A. No, it won't.

Well, first of all, I would need to read this paper, which I don't remember, certainly haven't read it in many months if at all.

Second of all, it would just tell me just like you asked me in the beginning of your cross-examination, it would just tell me that BHT unfavorably interacts with the active pharmaceutical ingredient, and that's why we have the type, the fact that the authors talk about here.

Q. And now, if someone came to you with another formulation in which they had added BHT and they found that it had no effect on the formation of oxidative degradation products, would that convince you it was not an antioxidant?

A. That very much depends on under what conditions they didn't observe it. Because as I was going to say, but you objected, but I presume that I can say it maybe now, I mean, in response to the question, that the second important rule when you carry out head-to-head tests is that you need to have sufficient oxidizing environment so

that the oxidation, the oxidative degradation without an antioxidant is significant, reliable measurable so that one can reliably ascertain whether a compound that is suspected to be an antioxidant indeed substantially reduces it.

If you have very little oxidative degradation, it is essentially impossible to determine, as Dr. Buckton said before lunch today, whether or not you have a reduction in the oxidative degradation. So I would need to see the data that led them to that conclusion.

Q. Dr. Klibanov, you have also provided the opinions to this Court that whether or not a compound is an antioxidant is not defined specifically by its ability to reduce oxidative degradation of rivastigmine; correct?

A. Yes.

Q. For example, a compound would be an antioxidant within the meaning of the '031 patent if it reduced oxidative degradation of an excipient; correct?

A. Yes.

Q. And you agree that there are thousands of excipients, and many categories of excipients;

correct?

A. There are a lot of different excipients, yes.

MR. BROWN: May I approach the witness?

THE COURT: Yes.

BY MR. BROWN:

Q. And, Doctor, you recognize that this is an exhibit you testified about during the Watson trial; correct?

A. I am familiar with this exhibit, yes.

Q. And running from page 111 to 116 of the reference are a long list of categories of excipients with a lot of examples; correct?

A. Yes, that's right.

MR. BROWN: Thank you, Dr. Klibanov. Par has no further questions.

THE COURT: Any redirect?

MS. JACOBSEN: Very briefly.

REDIRECT EXAMINATION

BY MS. JACOBSON:

Q. Dr. Klibanov, you were asked some questions about JTX 91. Do you have that paper in front of you?

A. Yes.

Q. Is that a paper about rivastigmine?

A. No, it's as follows from the title of the paper, I need to read the paper, but the title says peroxide oxidation of a thioester drug, rivastigmine is not a thioester.

Q. I believe you testified that that conclusion may suggest that the API, the active pharmaceutical ingredient in the paper was incompatible with BHT; is that right?

A. That's right.

Q. Have you seen any evidence that rivastigmine is incompatible with any antioxidants?

A. I saw no evidence to that effect.

MS. JACOBSEN: Thank you, Dr. Klibanov. I have no further questions.

THE COURT: All right. Dr. Klibanov, thank you. You can step down.

THE WITNESS: Thank you, Your Honor.

THE COURT: Does Novartis have anything more?

MR. KALLAS: No, Your Honor. But if you would like summation, we're ready to give you

one.

THE COURT: I thought we decided we weren't doing that. But hold on a minute, before we get there, Mr. Brown, does Par have anything more?

MR. BROWN: Nothing further, Your Honor.

THE COURT: All right.

MR. KALLAS: I don't know if we decided or not, it hasn't been mentioned.

THE COURT: I guess in a way I thought because I had booked it for two seven-hour days, not counting closing argument, I wasn't expecting it. I don't know, Mr. Brown, were you expecting it?

MR. BROWN: I was not expecting it.

MR. BROWN: I was not expecting it.

THE COURT: You know, so I appreciate the offer to stand up and talk, but I'm not actually sure that -- while I would not mind listening, I don't actually think it's probably fair to Par to do that since I don't think I don't have any evidence that they were

planning on doing that.

I assume, Mr. Brown, you'd like to pass on the opportunity?

MR. BROWN: Yes. I don't think it's the best use of parties or the Court's time.

THE COURT: Well, don't worry about my time.

MR. KALLAS: It would be a good use of our time, Your Honor.

THE COURT: Well, but really, Mr. Brown, it's up to you. Do you want to have some argument or not? I won't hold it against you no matter what your answer is.

MR. BROWN: I think, at this point, we prefer to proceed to post-trial briefing.

THE COURT: All right. Well, I think that, then, that's what we should do.

Do the parties have any exhibits that they have -- well, maybe you can -- is there anything -- are the parties sure that the trial is over?

MR. KALLAS: I believe so, Your Honor. We're going to check on the exhibits, so give us one moment.

MR. BROWN: Any reconciliation of the exhibits we can have with the court reporters.

THE COURT: So what kind of -- I'm sorry. And I forget these things, even though I know I've asked this before and I have been given the answer: Is Par the first filer?

MR. BROWN: Par is not. I believe the first filer, I believe it was -- Watson is the first filer.

But I don't think we have definitive information on that. That's just supposition.

THE COURT: Okay. All right.

So, oh, and I do have a question which is this: Did I understand the invalidity defenses from Par to be conditioned on a finding that the Par ANDA product infringes.

MR. BROWN: I believe that's correct, Your Honor. I believe that all of our 112 invalidity defenses are premised, they're alternative to acetaldehyde being found an antioxidant based on the evidence in this case.

THE COURT: I mean, that's what I thought I got from the way Dr. Buckman testified,

but I just wanted to make sure. I'm not sure that it actually affects anything in terms of briefing or anything else.

MR. BROWN: I'm fairly certain that that's all we've asserted. And --

THE COURT: I'm sorry. You're fairly certain what?

MR. BROWN: I'm fairly certain that that's all we have asserted as a defense.

THE COURT: So what kind of briefing schedule did you want to have?

MR. BROWN: We don't think a very long time is necessary. We haven't discussed this with our opponent, but we don't think a very long time is necessary.

THE COURT: I don't think a very long time. We have had something in the order of 12 hours, at least one of those was openings. So we had about 11 hours of testimony.

So what I'm -- and the court reporters, I'm sure, will have a transcript Monday or -- is that right? Tonight. Probably in a few minutes really.

So what I was thinking is I don't

really -- my suggestion would be this: At some point in time, which I would suggest might be two weeks from today, each side could submit a 20-page brief with Novartis' being you, Par, infringes. Par's being your patent's invalid for the three, 112 defenses we raised.

Two weeks after that, each side could submit a 20-page answering brief. And one week after that, each side could submit a ten-page reply brief.

And I would think that would probably cover everything in a reasonable number of pages. What do you all think?

MR. KALLAS: You're pretty close on the pages. I guess we could talk about that.

I was thinking of maybe five more pages. I was thinking maybe five more pages, Your Honor.

The timing poses a little problem for us. As you may recall, we agreed with the defendants in the other case to do some expert reports on June 5th. And you're asking us now to do all this work while we're working on those reports with the same team.

To avoid that, I would suggest a schedule, rather than two weeks, two weeks, one week, could we have three weeks, three weeks, one week or two weeks at the end, so I could stagger with that expert report?

THE COURT: Mr. Brown.

MR. BROWN: We're fine with that schedule.

THE COURT: All right. Well, you know, because Mr. Brown's fine with it, I'm sure that schedule will be fine.

MR. KALLAS: Thank you, Your Honor.

THE COURT: I mean, you know, I do see having seen four attorneys appear on your side -- well, in any event, why torture you? So it's okay, three, three and one.

All right. Well, so if you got the extra week, why don't you see if you can't fit it into 20 pages. Okay?

All right. Hold on a minute.

MR. KALLAS: Your Honor, may I address the issue of the page number? I know you said 20, 20, 10.

THE COURT: Okay.

MR. KALLAS: But they've had four witnesses on their side on infringement. The invalidity side is pretty small and certainly that would be more than enough.

But the reply brief of only ten pages, I would like a little more, Your Honor because, obviously, I'll be seeing their arguments, new arguments for the first time maybe.

And in terms of the law and cases, I may not be able to fit it in in ten pages. So I'd like a little more on that.

THE COURT: Mr. Brown.

MR. BROWN: We're amenable to that.

THE COURT: So what is it you want, Mr. Kallas?

MR. KALLAS: I'd like 20 pages, Your Honor, but I'll settle for 15.

THE COURT: All right. So you're okay with the 20 as opening, but you'd like 15 in reply?

MR. KALLAS: Yes.

MR. BROWN: We think ten pages is fine, Your Honor, no reason to go beyond that,

they already have their opening brief.

THE COURT: Well, I'll tell you what, you know, I'm not actually -- I will tell you what, I'll give you twenty-five in your opening brief, but I like to keep the reply at ten because as we have seen much evidence of over the last few days, or you just always have seen this, is the bigger the reply, the more that Mr. Brown is going to want to reply; right?

So put into your opening brief the creative arguments, because after you don't really need to repeat in the reply what you said in the opening. If it really comes up stuff that is out of left field, you know, you will meet and talk about it and see whether we can work something out, if not, you can give me a phone call. But I think ten is enough on the reply.

But you have twenty-five on infringement for the opening brief, so therefore you want twenty-five to answer, you can have that. Okay.

Hold on a minute.

MR. KALLAS: Your Honor, as Mr. Brown and I have agreed for the infringement

side will be twenty-five, twenty-five if he wants it and ten for the validity side which is much smaller, it would be twenty, twenty and ten.

THE COURT: All right. That's what I was -- that's good. Hold on a minute. The other thing that I'm just wondering about here is do you recall when we had the claim construction hearing a year-and-a-half ago or whenever it was we had it, as I recall it the main dispute on antioxidant was whether or not it had the function, that that was part of the limitation. And that basically because of claim differentiation, there was some claim where it was clearly written in. I said you didn't -- the antioxidant by itself didn't have the functional aspect so that's the reason why we have presence claims and functional claims, and of course the only claim that we have been trying here is the presence claim.

Was that the main dispute of the claim construction hearing, if you remember?

MR. KALLAS: Your Honor --

THE COURT: And Mr. Kallas, probably it was Mr. Prugo.

MR. KALLAS: I don't remember exactly what the main dispute was. I know that was a major dispute. I know we have had -- what I can't do, Your Honor, is separate the dispute we have had in this case with the recent dispute we have had in the claim construction with Noven and Algen, so I'm not certain who argued what when.

THE COURT: So let me just tell you what I was thinking about was I can't tell, you did -- there is an order that's in the book that you handed up with I think it was Dr. Klibanov's testimony which was the order entered June 21st, 2013 that followed the claim construction hearing.

And what I'm wondering about is whether there was a focus that should have been on whether essentially the way I construed it, agent reduces oxidative degradation, whether that was what a person of ordinary skill in the art would have understood as an antioxidant, and I'm wondering actually how much dispute there was between the parties over that portion.

I know Par wanted to have this

functional thing added in. I'm not trying to revisit that. But I was just wondering whether what I ended up with wasn't perhaps broader than it should have been. And so not wanting to revisit the functional issue, and now having the understanding after having had the trial as to what the -- having a better understanding of the science that goes along with this, I'm just wondering whether there is some narrower interpretation that I should have been giving to antioxidant, and particularly whether a person of ordinary skill in the art would have thought that antioxidant was essentially -- and if the -- if essentially I did get it right, agent reduces oxidative degradation, whether there are any limits in the sense of is this something, you know, if an agent can reduce oxidative degradation in one unique circumstance, somewhere you can find out in the chemical world, does that make it an antioxidant, or maybe should I have -- I don't remember whether this was actually something that was discussed in the claim construction or not. Possibly it was and it didn't impress me at the time.

But whether things like the pharmaceutical handbook saying here is what the antioxidants are, you know, whether that suggested some more limited definition might have been appropriate. So I don't know. I can't help you any more than that, which may not help at all.

But what I was going to say is -- well, other than saying I'm having some second thoughts I guess about that definition. I don't really have anything more to say. I am having some second thoughts. And if there is something that you all either have to say right now or you want to think about and talk to each other, you should let me know, I guess.

Is there anything either you want to say right now?

MR. BROWN: Your Honor, we would just propose that we can include that in the twenty-five page briefs that the parties submit and/or we could -- if it would make sense since we have a three-week period for the opening brief, if we want to exchange with each other proposed narrowing claim construction, maybe we

could do that in two weeks so that everybody knows what position they have.

THE COURT: Mr. Kallas.

MR. KALLAS: Well, you know, we tried the case on your claim construction. So now if you're going to change the claim construction, I think that would be unfair to us.

If you want it rebriefed, Your Honor, we're happy to rebrief it. We'd have to work out another schedule. I'm not certain it's going to fit in the pages we presently have, though.

THE COURT: I'm sorry. Can you speak up?

MR. KALLAS: Yes. I'm not -- if you want it rebriefed, obviously, we'll rebrief it, Your Honor. But I don't think it will fit in with the number of pages you've given us and the short reply time, because then I will see their position and I have one week to respond by. I think it will be unfair.

THE COURT: Well, I think that's right. So why don't we do this: Because I'm

guessing that Mr. Kallas would likely be perfectly happy with the construction as it stands right now.

And it might be Mr. Brown who says, Geez, I hear something that interests me here. So, Mr. Brown, why don't you and your people think about it and if you've got some different construction that you think is better and that there's support for, why don't you, by the close of business on Tuesday, tell Mr. Kallas what it is, and what your support is and then he can go from there.

MR. BROWN: We can do that, Your Honor.

MR. KALLAS: I guess one problem that Dan Silver reminds me, you know, we tried the Watson case under this claim construction. I have think you gave it the same claim construction in --

THE COURT: Well, I'm sure I did.

MR. KALLAS: -- the Noven case. And as soon as we leave, we're going to serve our reports in that case. So we have a lot of things in the air here.

And changing the construction at this point may change all of those things.

THE COURT: Well, I can only deal with so many things at once. You know, part of the -- so, and if I didn't -- yes, Mr. Silver, you want to --

MR. SILVER: Can I whisper it to Mr. Kallas?

MR. BROWN: Maybe I can --

THE COURT: Well, wait a second. Let them whisper.

MR. KALLAS: As I recall, in this case, Your Honor, we were on Judge Robinson's schedule where claim construction came later in the case, not on your schedule, where it comes early in the case. So all the contentions were out there.

They have the opportunity to argue the claim construction knowing all of what our infringement allegations were, I believe. So I'm not certain.

THE COURT: Well, so all right. Mr. Brown, you wanted to say something?

MR. BROWN: Just certain I think

some of these concerns are being -- are not as big as they're being presented to be. In the Watson --

THE COURT: Well, they're not as big for you. They are as big for them because they've got lots of different --

MR. BROWN: I'm not underestimating the impact on them. I mean, as far as inconsistencies or things between cases in the Watson case, BHT, the product at issue, was in the ANDA pharmaceutical example in the patent. And nothing is -- nobody is going to be proposing conflicting claim construction. It's just a more precise claim construction that would address issues that are in this case.

And such that I don't think would have any impact on the Watson case, one way or another or would change the evidence they presented.

THE COURT: And that's not something -- so I hear what you're saying. And I heard what Mr. Kallas said. And I appreciate where he's coming from.

And so all I guess I would say is it

does seem like the case that, as far as claim construction goes, sometimes the fact that claim construction doesn't become a fixed thing at any particular point in time can cause some inconvenience. And it may be that with some further looking, nothing will change. I don't know.

But I at least -- because, as Mr. Brown says, I think in the other case, the Watson case, I do think, as I recall, BHT is in the pharmaceutical handbook as an antioxidant. So the definition of antioxidant, it didn't come up the way that it's come up here where, you know, I'm hearing that an antioxidant is something that pharmaceutical references don't call an antioxidant. And it starts to make me wonder: Did I construe this too broadly?

MR. KALLAS: If I may, Your Honor, help, Your Honor. I think we -- my recollection, I'm trying to separate the two, the present case and the past case. The present case being the Noven case, I believe.

And it was based on the slide that was put up on the parties' competing claim

constructions, the Watson-Par defendants wanted it to be a pharmaceutically acceptable ingredient, which may have meant you go to the Handbook of Pharmaceutical Excipients.

We argued that it is not. It just had to be in a composition that was going to be approved at the FDA.

So I think this issue whether it has to be in a pharmaceutical book, and it has been litigated and Your Honor chose that you didn't like that.

THE COURT: Okay. Well, you know, and --

MR. KALLAS: If that's where you're going with this.

THE COURT: I'm not really sure. I'm not necessarily going anywhere.

But I -- but, you know, that's -- but so what I'm going to do is I'm actually going to try to retrieve which may -- which may actually be more difficult because I imagine when we did this, that was when sealed documents were not actually available to me electronically, so trying to get hard copies of things are that much

more aggravating. But it may be because this thought, you know, which sort of, I first started wondering about this at lunch time, and so I haven't actually checked to see what happened, and I gather you have somebody who knows for one reason or another.

MR. KALLAS: I just recall from the slide that was put up to cross-examine Dr. Buckton it had ours and there's and there's was a pharmaceutically acceptable ingredient that had to be added to the composition. And we argued against that just for this reason, Your Honor, and Par was involved, they were represented. So I think it's been --

THE COURT: But, you know, in any event here is what I'm going to do. I'm going to spend a little time this afternoon trying to figure out what I knew a year-and-a-half ago, or what I thought I was dealing with a year-and-a-half ago, and maybe this concern will go away. But I'll do something if not, and maybe not by the end of today, but as soon as I figure out whether I do or do not have this concern, I'll call Mr. Fineman and Mr. Silver and let them

know. And if I call them and say sorry, I got my problems resolved, then just give me a heart attack for no reason. And if I say no, I still have some concerns, then Mr. Brown can tell you how he would like to construe it and --

MR. KALLAS: Just any claim construction we have had, both sides have put in expert reports, so it may not be as simple as just file a brief, because our expert reports may not raise the new issues that Mr. Brown, or prior ones, so I'm not certain how this will work. Let's see if you have a concern and we'll go from there.

THE COURT: Let's see if I have a concern and you all can go from there.

MR. KALLAS: We'll work it out.

THE COURT: Hopefully. Anything else?

MR. BROWN: No, Your Honor.

THE COURT: All right. Well, thank you for all your time and attention. And I will go back and start working on this little problem.

And thank you very much. Have a good weekend.

(Court ended at 3:37 p.m.)

State of Delaware)
)
New Castle County)

CERTIFICATE OF REPORTER

I, Heather M. Triozzi, Certified Professional Reporter, Registered Professional Reporter and Notary Public in the State of Delaware, do hereby certify that the foregoing record, Pages 347 to 631 inclusive, is a true and accurate transcription of the above-referenced proceeding on the 2nd day of May, 2014, in Wilmington.

IN WITNESS WHEREOF, this 2nd day of May, 2014, at Wilmington.

/s/Heather M. Triozzi, CSR, RPR
Heather M. Triozzi, CSR, RPR
Cert. No: 184-PS
Exp: Permanent

DATED: May 2, 2014

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